DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

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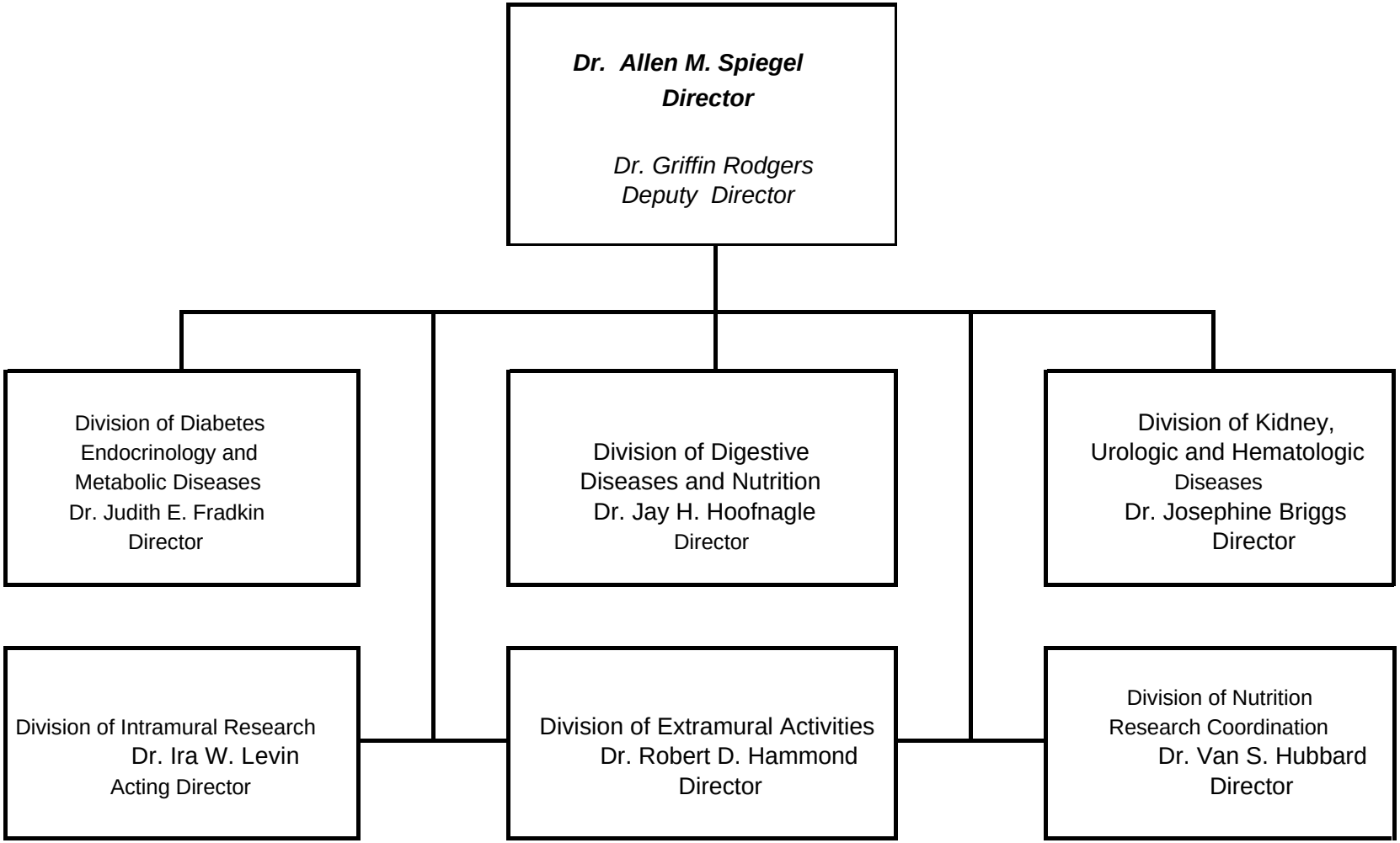
Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

For carrying out Section 301 and Title IV of the Public Health Service Act with respect to diabetes and digestive and kidney diseases, [1,303,385,000] *$1,457,915,000*.

[Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriation Act, as enacted by the Omnibus Consolidated and Emergency Supplemental Appropriations Act for Fiscal Year, 2001, (P.L. 106-554)]

National Institutes of Health

National Institute of Diabetes and Digestive and Kidney Diseases

Amounts Available for Obligation 1/

Source of Funding	FY 2000 Actual	FY 2001 Estimate	FY 2002 Estimate
Appropriation	$1,147,588,000	$1,303,385,000	$1,457,915,000
Enacted Rescission	(6,112,000)	(429,000)	---
Subtotal, Adjusted Appropriation	1,141,476,000	1,302,956,000	1,457,915,000
Real transfer to:			
Other NIH Institutes through the NIH Director's one-percent transfer authority	(957,000)	---	---
Other HHS Agencies through Secretary's one-percent transfer authority	(239,000)	---	---
HHS for the Office of Human Research Protection	---	(272,000)	---
Real transfer from:			
State Children's Health Insurance Program in the Health Care Financing Administration for Type I Diabetes Research	27,000,000	---	---
Comparative transfer to:			
Other NIH Institutes as a result of a change in assessment formula for Central Services funding	(61,000)	---	---
Comparative transfer from:			
Office of the Director for the Academic Research Enhancement Award program	1,087,000	1,133,000	---
Subtotal, adjusted budget authority	1,168,306,000	1,303,817,000	1,457,915,000
Unobligated balance lapsing	(170,000)	---	---
Total obligations	1,168,136,000	1,303,817,000	1,457,915,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2000 - $8,286,000 FY 2001 - $8,250,000 FY 2002 - $8,350,000
Excludes $ 869,244 in FY 2000 and an estimated $900,000 in FY 2001 for royalties.

Justification

National Institute of Diabetes and Digestive and Kidney Diseases

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Authorizing Legislation: Section 301 of the Public Health Service Act, as amended. Reauthorizing legislation will be submitted.

Budget Authority:

FY 2000 Actual		FY 2001 Estimate		FY 2002 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
599	$1,168,306,000	627	$1,303,817,000	649	$1,457,915,000	22	$154,098,000

This document provides justification for the FY 2002 activities of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2002 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

Introduction

The NIDDK conducts and supports research on many serious and costly diseases affecting the public health. Several diseases studied by the NIDDK are among the leading causes of disability and death in the Nation; all seriously affect the quality of life of those suffering from them. The economic burden of these diseases represents a major proportion of U.S. health care expenditures. A focus on basic research has traditionally guided the Institute's programs. A fundamental understanding of biologic systems will ultimately explain the abnormalities underlying disease and thus is imperative for the development of the most effective strategies for prevention and therapy. In addition to basic research, the Institute has a strong commitment to expand advances in the understanding of disease processes into appropriate clinical studies and ultimately into efforts to transmit knowledge and effective technologies to practicing physicians.

The NIDDK's Division of Diabetes, Endocrinology, and Metabolic Diseases is responsible for extramural research and research training related to diabetes mellitus; endocrinology, including osteoporosis; and metabolic diseases, including cystic fibrosis. The Division of Digestive Diseases and Nutrition has responsibility for managing research programs related to liver and biliary diseases; pancreatic diseases; gastrointestinal diseases, including motility, immunology, and digestion in the gastrointestinal tract; nutrient metabolism; and obesity, eating disorders, and energy regulation. The Division of Kidney, Urologic, and Hematologic Diseases supports research on the normal and disease processes of the kidney, genitourinary tract, and the blood-forming organs to improve or develop preventive, diagnostic, and treatment methods. The Division of Intramural Research conducts research and training within the Institute's laboratories

and clinical facilities in Bethesda, Maryland, and Phoenix, Arizona. Shared interests in the biochemical and genetic processes underlying disease link the programs and divisions of the Institute, while close communication between the NIDDK and other NIH programs also fosters a confluence of fundamental knowledge in these vital areas of investigation.

Science Advances

Genetics, Genomics, and Bioinformatics

Gene Expression of Genomic Sites–Imprinting: In a process called "imprinting," the genes from only one parent's chromosome are expressed. One of the two copies of a gene is switched "off," while the other is switched "on." Imprinted genes are often associated with human diseases, including disorders affecting cell growth, cell development, and cell behavior. The transcription of imprinted genes makes it clear that a mechanism superimposed on traditional genomic and genetic principles, called "epigenetic," restricts gene expression and offers a model for understanding the role of chromosomal DNA structure and its modifications in regulation of gene expression. For insulin-like growth factor 2 (IGF2), scientists have now discovered insulators of gene expression. They report that a certain protein (called CTCF), acts to prevent the gene from making IGF2. Further studies showed that DNA near the IGF2 genes of mice and humans did indeed contain binding sites for CTCF. Using cells in culture, researchers next showed that these binding sites can only block the action of an "enhancer" on the gene when the binding sites lie between the enhancer and the gene, a signature of insulator activity. In the case of the IGF2 gene, the protein binding sites are found in the same region of DNA that has methyl groups on the paternal, but not maternal, copy of the gene. In the final experiment, the team showed that adding methyl groups to the DNA binding sites for this protein prevents further binding of the protein. This finding strongly suggests that methylation abolishes the insulating capability of the protein on the paternal copy of the gene. As a result, the enhancer can activate paternal gene expression. The research demonstrates that the control mechanism for insulating against the activity of this imprinted gene is a novel "boundary" element, which the investigators call the "imprinting control region." Also, the fact that protein binding, and therefore insulator activity, can be turned "on" and "off" by changing the methylation state of DNA suggests that there may be many other places in the genome where a similar mechanism suppresses expression of a gene. New knowledge generated from studies of imprinting opens important avenues for potential treatment and prevention of a wide range of genetic diseases.

Novel Approaches in Gene Transfer Delivery Methods: Gene transfer is a novel approach to selectively alter the expression of a person's genes in an effort to treat, cure, or ultimately prevent disease. One of the greatest challenges in gene transfer is to develop ways to deliver therapeutic materials to the cells of a patient in a way that is specific, efficient, and safe. Viral-based vectors that have shown potential as vehicles for gene delivery include: adenovirus, herpesvirus, retrovirus, and adeno-associated virus (AAV). Until recently, the use of AAV vectors has been limited by the size of the genetic material that can be incorporated into the vector. Diseases caused by defective genes with coding regions larger than the AAV capacity, such as Hemophilia A or Duchenne muscular dystrophy, have not been amenable to therapeutic studies using the AAV vector systems. Now, NIDDK-supported researchers have demonstrated that the

application of genetic engineering methods can enable recombinant AAV vectors to be used to deliver the larger therapeutic genes. Three groups have independently developed methods to split a gene's coding region into two such AAV vectors that are then reassembled in the cell. This finding will significantly increase the usefulness of the recombinant AAV vector for gene therapy of inherited and acquired diseases. In other studies of gene delivery systems, NIDDK-supported researchers are examining the use of DNA alone–called "naked" DNA–as an alternative to the use of viral vectors. One approach to enhance gene expression is to incorporate into the vector parts of DNA called "transposons," which are naturally occurring genetic elements capable of moving from one genetic location to another, often by a "cut and paste" mechanism. The transposons may permit lifelong gene expression with a single administration of the vector. Thus, the use of transposons represents a major advance in the development of stable nonviral gene transfer systems.

Cause of Kidney Stones: Abnormally high absorption of calcium in the intestine, called absorptive hypercalciuria, is a common cause of kidney stones. Studies of families with a history of kidney stones indicate that an inherited genetic defect is one likely cause of this condition. Researchers now have identified a specific region on chromosome 1 that is associated with a severe form of the disease. Scientists are pursuing identification of the gene and its mutations, which, when known, may permit early diagnosis of the abnormal absorption of calcium and the possible prevention of kidney stones in this group of patients.

Pinpointing Genes for Kidney Disease of Diabetes: Diabetes is the most common cause of end-stage kidney disease in the U.S. In diabetes patients, even modest amounts of protein in the urine increase the risk of progressive kidney disease, as well as cardiovascular complications. However, understanding the heritable components of complex genetic diseases such as kidney disease and diabetes is proving to be a major challenge. Recent studies provide evidence that protein in the urine is a good marker of disease susceptibility, independent of additional factors that may increase the risk of kidney disease. Research suggests that one major gene may increase susceptibility to the kidney disease of diabetes, at least in the Pima Indian population, which increases confidence in the feasibility of eventually identifying that gene. These findings help to establish a foundation for future genetic analyses of kidney disease, particularly that caused by diabetes, in Caucasian and Pima Indian populations.

New Insights Gained into Genetics and Treatment of Polycystic Kidney Disease: Using three mouse models of polycystic kidney disease (PKD), scientists have found that, depending on the severity of the mutation, the animals either died before birth of major kidney, heart, and pancreas defects, or had decreased length of survival. They concluded that the presence of a protein, called polycystin-2, is essential for normal development of parts of the kidney, heart, and pancreas. A second research team examined kidney cysts from two patients and discovered that almost three-fourths of the cysts had mutations in one PKD gene, while a subset of cysts lacked that particular mutation, but had mutations in another PKD gene. The findings suggest that mutations in the former PKD gene may be modifiers of disease severity, and that independent disturbances in the production of the polycystin proteins by the PKD genes may be sufficiently disruptive to cause cyst formation. In another series of experiments, researchers built upon recent insights in cell signaling mechanisms to show that a newly-developed inhibitor of epidermal growth factor

receptor tyrosine kinase activity reduced the size and number of cysts, improved kidney function, decreased liver abnormalities, and increased life span in a mouse model. The drug acts on an enzyme critical for growth factor signaling. When drug treatment was stopped, the disease returned. In addition to increasing the knowledge base with respect to how to identify and treat complications of PKD, the earlier breakthrough discovery of PKD genes has also opened new avenues of research on the most prevalent form of the disease. These include the determination of the proteins produced by the genes and how they function in the normal and disease states, and the interactions of the abnormal genes that lead to disease. These research avenues will advance understanding of the molecular and cellular events in PKD, so that safe and effective therapies can be developed. In addition, further research on growth factor signaling pathways could form the basis for starting human trials leading to an effective treatment for PKD.

Simple System Yields Clues About Anemia: The zebrafish is an animal model that is being used increasingly to study genetics, development, and disease. Investigators report identification of a mutant zebrafish gene that results in a type of anemia during embryonic development. The gene, named *ferroportin1*, normally produces a protein that transports iron out of cells. Because of a mutation in *ferroportin 1*, the function of this protein, which also is found in mammals, may be perturbed in disorders such as iron deficiency anemia or iron overload disorders, such as hemochromatosis. The insights gleaned from this research open up a new avenue for the development of potential treatments for this group of genetic blood disorders.

Developmental Biology

Research on the very earliest stages of cell and organ development is providing a wealth of knowledge from which new approaches for treating and preventing disease will emerge. Two key areas are extremely promising. First is the study of adult human and animal stem cells, which have remarkable properties of replication and differentiation that may provide a means to repair or replace a host of diseased tissue and organs. Adult stem cells hold exceptional promise for advances in medical care because they appear to be able to give rise to many different types of specialized cells that could be used for therapeutic purposes. One such type of highly versatile stem cell that may be "coaxed" to differentiate into a broad range of organ-specific cells is called a "hematopoietic" stem cell. These cells originate in the bone marrow and the liver. In one recent study, researchers used specific markers to separate all of the hematopoietic and lymphoid progenitor cells from mouse bone marrow cells, and then to study the remaining sub-populations of cells. In this way, they found a common myeloid progenitor cell in the mouse–a discovery that will help to advance stem cell research. In a related study, researchers reported using a combination of analytic techniques to elucidate novel stem cell genes in fetal mouse liver tissue. From extracted cells, they identified genetic factors involved in direction of protein synthesis. They also identified cell surface molecules, secreted proteins and signaling molecules. Many of these were previously undescribed or were found in stem cells for the first time. These types of studies set the stage for future investigations of genes involved in the commitment of cells to specific lineages and also for investigations of the transformation events leading to the multitude of blood disorders. Moreover, the discovery of stem cell proteins will facilitate the study of networks of protein interactions, known as proteomics. This knowledge will be critical for future research that can produce specialized cells for treating disease.

A second research avenue that offers important clues about early developmental processes is study of the zebrafish as a model system for understanding abnormal organ development and how it might be corrected or prevented. Investigators participating in a major NIH-wide research initiative are mapping the genome of the zebrafish, whose properties make it an amazing research tool. Because the zebrafish embryo is transparent and has a relatively long life span, researchers can actually visualize its earliest cellular differentiation and subsequent organ development. Now, they are actively involved in uncovering the genetics of the zebrafish for what it may reveal about genetically-based developmental disorders in man.

Harnessing Technology

Development of a Novel Technique To Analyze Membrane Proteins: The ultimate product of gene expression is a mature protein, formed according to the instructions held within DNA. Therefore, errors in DNA sequence that lead to improper protein structure are responsible for many disorders. Because each protein is made up of a unique combination of amino acids, detailed knowledge of a protein's size is an important tool in identifying it and detecting any errors in its composition. One group of proteins has proven resistant to most traditional approaches to size determination: "transmembrane" or "membrane-bound" proteins, which comprise about ten percent of all proteins within a cell. These proteins are partially embedded in the layer of fat which makes up cellular membranes. They often play important roles as hormone receptors, channels that permit small molecules to cross in and out of the cell, and mediators of other critical cellular functions. Investigators have developed a widely-applicable technique that permits the rapid determination of the molecular mass of a full-length membrane-associated protein with high precision. This technique can be used to identify new proteins, to detect small errors in the amino acid sequence of known proteins, and to characterize important chemical modifications to proteins that occur after assembly. Importantly, it can also be used to identify new proteins in a crude tissue preparation without extensive purification, a step that has often proven difficult and time-consuming. The completion of the Human Genome Project, as well as the continued sequencing of animal genomes, will lead to the identification of a number of proteins of unknown structure and function. The ability to determine the size of these proteins accurately and quickly will allow more rapid identification and characterization of these new proteins and will assist in analysis.

A Useful Technique for Understanding Signaling in the Cell: Cells communicate with each other through extracellular signals. Signals received by cells may also penetrate within the cell through a series of intracellular pathways. Both inter-cellular and intra-cellular communication are critical for maintaining normal functions; disruption of cell signaling pathways can lead to disease. In order to treat diseases resulting from failures in cell signaling, researchers must first understand the order of steps in a signaling pathway and how the steps are related to each other. One way to study the order of signals is to remove a signal (or "knock it out") and observe the effect of its absence, noting which steps are disrupted and which occur normally. This permits a researcher to determine the order of events in a given pathway. In the past, creating knockouts in cell cultures was relatively inefficient and could result in physiologically abnormal conditions. Recently, scientists discovered that the addition of double stranded RNA (a protein precursor) to a cell culture interferes with production of the protein derived from that RNA, resulting in a

protein "knock out" in the cell culture. This technique, called double-stranded RNA-mediated interference, or RNAi, appears to eliminate 95-99 percent of the targeted protein. Because it can elucidate the precise functions of signaling pathway components, RNAi may provide information necessary to treat diseases resulting from cell signaling disruption, such as type 2 diabetes in which insulin signaling is abnormal. In addition, use of RNAi may enable investigators to assign roles to the enormous numbers of presumed signaling proteins identified in the Human Genome Project.

Imaging Technology: The most important clinical feature of polycystic kidney disease (PKD) is the progressive enlargement of cysts in the kidney, a process that in many patients results in gradual deterioration of renal function and ultimate renal failure. Currently, no good means exist to test whether or not a potential therapeutic intervention will alter the course of the disease. This represents a major barrier to clinical studies to assess the effectiveness of potential therapeutic agents in altering progression of the disease. To address this problem, the NIDDK is supporting a major study to develop innovative imaging to evaluate progression of PKD. This research initiative is encouraging studies to identify and test the accuracy and reproducibility of medical imaging techniques, as well as the identification of surrogate markers of disease progression, which should lead to the planning and testing of clinically appropriate interventions for PKD. The primary goal is to test whether imaging techniques can provide sufficiently accurate and reproducible markers of progression of renal disease in PKD to permit their use in clinical trials. The Institute plans to add ultrasound imaging methods and to increase the investment in image processing algorithms. Along with a second activity that established four Specialized Centers for Polycystic Kidney Disease Research, these studies should foster and extend the development of new approaches into the causes, early diagnosis, and improved treatments for PKD. The products of this research should speed the pace at which clinical studies can evolve.

Minority Health Disparities

Diabetes, obesity, hepatitis C, end stage renal disease, benign prostate disease and other diseases within the NIDDK research mission place a disproportionately heavy burden on racial and ethnic minority groups. To intensify efforts to redress these disparities, the NIDDK has established a new Office of Minority Health Research Coordination, which has developed a comprehensive Strategic Plan of proposed goals and implementation strategies. Examples include:

Diabetes Prevention Program: The NIDDK is making plans to build upon its Diabetes Prevention Program -- a major, multi-center clinical trial slated for completion in FY 2001. Designed to test lifestyle and pharmacologic intervention strategies in individuals at risk of type 2 diabetes, this trial has extensive minority representation. Nearly 45 percent of participants are African American, Hispanic, Asian American, Pacific Islander, or Native American.

Type 2 Diabetes in Children: New research initiatives focus on understanding and combating the alarming increase of type 2 diabetes in children, which is particularly prevalent in minority children. This research is being intensified as part of the Institute's overall commitment to stem the tide of type 2 diabetes, which is reaching epidemic proportions in the United States.

National Diabetes Education Program: In a collaboration with the Centers for Disease Control and Prevention and approximately 150 partner organizations, this program is increasing diabetes awareness and helping patients manage their diabetes and its complications. Minority groups participating in this program are developing public education messages tailored to the cultures of their specific target audiences.

End-Stage Renal Disease in African Americans: The NIDDK is continuing to build upon one of its major clinical trials, the African-American Study of Kidney Disease and Hypertension. Recently, the NIDDK released the trial's findings earlier than planned because of their immediate therapeutic importance. The trial found that calcium channel blockers are less effective than either angiotensin-converting enzyme (ACE) inhibitors or beta blockers as a first-line treatment for hypertension–a message that must be translated to medical practice as rapidly as possible. The trial will continue in over 1,000 African Americans at 21 research centers in order to compare ACE inhibition and beta blocker therapy to determine whether the lower-than-usual blood pressure target is more beneficial to the kidneys.

Diabetes

As the lead Federal agency for diabetes research, the NIDDK is pursuing vigorous efforts to combat this disease and its health complications. Diabetes is the leading cause of new adult blindness, kidney failure, and non-traumatic amputation, and is a major risk factor for stroke, heart attack, and premature death. In type 1 diabetes, sometimes called juvenile diabetes or insulin-dependent diabetes, the body's immune defense system destroys the insulin-producing cells in the islets of the pancreas. Daily injections of insulin are necessary to sustain life, and compliance with this treatment regimen is extremely difficult. In type 2 diabetes, the pancreas usually produces insulin, but, because the body cannot use this hormone effectively, an unhealthy buildup of glucose occurs in the blood. Type 2 diabetes is the most prevalent form of the disease, and is more common in older people–especially those who are overweight–and among minority groups.

Role of the Immune System in the Development of Type 1 Diabetes: One of the first signs of an immune response is the production of antibodies–proteins that help the body in the detection and removal of foreign agents that threaten health. In individuals with type 1 diabetes, this immune response is abnormal and patients develop antibodies against proteins in their own insulin-producing pancreatic cells, including insulin itself. A recent study showed that elevated insulin autoantibodies in infants seems to predict subsequent onset of type 1 diabetes. This finding adds another dimension to existing knowledge regarding ways to identify individuals at risk for the development of type 1 diabetes and could thus be instrumental in facilitating the study of novel interventions before irreversible damage occurs to the insulin-producing cells in the pancreas. The NIDDK is launching a network of clinical trial sites, called TrialNet, for type 1 diabetes, so that new treatment and prevention strategies can be tested as rapidly as possible. In related research, scientists are studying a group of proteins on the surface of immune cells that may help identify potentially harmful antigens. In mice susceptible to type 1 diabetes, the researchers found that one component of this protein complex, which is called the "Major Histocompatibility Complex (MHC)," differed from that found in normal mice. This difference resulted in a different shape

that may cause the protein complex to mis-identify normally occurring benign proteins as threatening. Subsequent studies have shown that molecules containing this change can assume several alternative conformations, depending upon the nature of protein interactions, and that the range of proteins with which the MHC could interact was different, depending on whether it was derived from a normal or a diabetic mouse. Some individuals with type 1 diabetes have a MHC whose structure is similar to that of the diabetic mice, which suggests that a similar mechanism may lead to development of type 1 diabetes in both animals and humans with this characteristic.

Overcoming Obstacles to Islet Transplantation for Type 1 Diabetes: The NIDDK has a strong program of research on islet cell transplantation as a potential cure for type 1 diabetes. For example, it is helping to support a multi-center research effort to replicate a highly promising clinical research protocol that has enabled at least seven people with type 1 diabetes to remain independent of exogenous insulin injections for over a year following the transplantation of islet cells. While this impressive research continues, the NIDDK is also working to address other obstacles. Unfortunately, the availability of a sufficient number of islet cells for transplantation and the means to prevent their rejection without long-term drug treatment to suppress the immune system are prerequisites to making islet transplantation a reality for patients with type 1 diabetes. In efforts to overcome the inadequate supply of islet cells, scientists demonstrated that pancreatic tissue from both humans and mice could be cultured to produce islet-like clusters of pancreatic endocrine cells able to release insulin in response to glucose. In addition, these cells could restore insulin production and normalize blood glucose in a mouse model of diabetes. In a related line of research, NIDDK-funded investigators are trying to overcome the toxicity that immunosuppressive drugs can cause to transplanted islets, as well as the increased susceptibility to infections and malignancies. They are exploring an alternative to long-term immunosuppression called "tolerance induction," which is an innovative approach for teaching the immune system to accept foreign tissue as "self." In a recent study, investigators transplanted islets isolated from the pancreas of non-diabetic monkeys into the portal vein of diabetic monkeys. Instead of receiving a regimen of long-term immunosuppressive therapy, the monkeys were treated with a tolerance-inducing medication for only four days following surgery. After recovery, the animals achieved control of blood glucose and, nine days following the transplantation, none of them required insulin injections. Advances such as these represent major steps toward achieving the reality of a "cure" for type 1 diabetes.

Genetics of Type 2 Diabetes: Type 2 diabetes is thought to arise from genetic factors, combined with environmental factors, such as obesity. More than one genetic alteration or mutation is probably necessary for development of type 2 diabetes, which is therefore considered a "complex" genetic disease. Researchers have now found what they believe to be the first gene that predisposes individuals to this disease. Designated *NIDDM1*, the location of this gene was first narrowed to a particular genetic region in a population of Mexican Americans, who are known to be particularly prone to type 2 diabetes. Now, within that region, researchers have definitively pinpointed the *NIDDM1* susceptibility gene. They have also discovered that this gene encodes an enzyme that is a member of the calpain-like cysteine protease family, Calpain 10. The demonstration that this enzyme is present in pancreatic islet cells, muscle, and liver strongly suggests that it may affect insulin secretion, insulin action, and glucose production, each of which is altered in patients with type 2 diabetes. Scientists believe that *NIDDM1* may interact with a

yet-to-be discovered gene on chromosome 15 to increase susceptibility to type 2 diabetes. This extraordinary progress in unraveling the complex genetic mysteries of type 2 diabetes implicates a new biochemical pathway in the regulation of blood glucose that could be enormously important in providing new targets for the development of novel therapeutic and prevention strategies. In other research on the genetics of type 2 diabetes, scientists have implicated other genes that may play a causative role in the disease. Mice that have been genetically modified in the laboratory to "knock out" the *NEUROD1* gene have abnormal pancreatic islets and develop overt diabetes, due in part to inadequate expression of the insulin gene. Interestingly, mutations in this gene have also been found in two families with type 2 diabetes. Investigators have also found mutations in the insulin promoter factor-1 gene, known as *PDX-1*, which is critical for proper development and function of the pancreas and thus may be related to the development of type 2 diabetes. Although *PDX-1* has been previously implicated in the development of a rare form of diabetes known as Maturity Onset Diabetes of the Young, this is the first report that it may also be involved in the more common form of type 2 diabetes. Other studies have revealed a region on chromosome 12, called *NIDDM2*, which may contain a gene that, in combination with other factors, predisposes individuals to type 2 diabetes. All of these research findings are converging to strengthen the knowledge base about the genetics of type 2 diabetes and thus pave the way to improved diagnosis, treatment and prevention. The NIDDK will continue to capitalize on these remarkable advances, which could provide the means to stem or even reverse the increasing incidence of this devastating disease.

Insulin Receptors and Insulin Signaling in Type 2 Diabetes: To understand more completely how insulin exerts its effects on target cells, and how cells might lose the ability to respond to it, scientists have studied mice in which several proteins important in the insulin signaling pathway are either completely absent, or are present in diminished levels. Mice with different combinations of signaling proteins at lower than normal levels develop diabetes at similar rates. However, subtle differences can be detected in which tissues exhibit defects in insulin signaling and in the severity of the impairment. Furthermore, pancreatic beta cells taken from mice completely lacking one signaling protein contain less insulin than normal cells, and they also exhibit defects in insulin secretion. These studies emphasize that the responsiveness of a given tissue to changes in glucose levels is complex, and requires the coordination of multiple proteins. Each member of the signaling pathway seems to perform unique functions that cannot be fully replaced by another. This uniqueness of function lends support for the view that type 2 diabetes is an inherited disease in which many genes may play a role in disease onset and progression.

Type 2 Diabetes in Children, Adolescents, and Young Adults: An alarming rise in the incidence of type 2 diabetes in children is occurring largely in minority populations–Hispanic Americans, African Americans, and Native Americans–and the increase of obesity in these same populations is an important risk factor. These trends pose a new and challenging clinical problem for

pediatric specialists because little is known about the clinical management of type 2 diabetes in childhood and adolescence. Thus far, children have been treated with several different approaches, including diet, oral agents to control blood glucose levels, and insulin. Yet, scientific data are needed to support these strategies and develop more refined ones. Additional research is being vigorously pursued to yield reliable methods for early diagnosis, the development and testing of therapeutic agents for safety and efficacy, and a better base of scientific knowledge as a foundation for education programs.

Walking Reduces the Risk of Type 2 Diabetes in Women: Obesity and reduced physical activity are major risk factors for the development of type 2 diabetes. People at risk for developing this disease therefore are encouraged to maintain a healthy diet and engage in regular exercise. Studying a cohort of women previously identified through the Nurses' Health Study, researchers found that moderate forms of exercise, such as walking, and vigorous forms of activity, such as aerobics, are both associated with a substantial reduction in risk of type 2 diabetes in women. This finding is a practical approach to prevention because walking is a form of exercise that is highly accessible, readily adopted, and rarely associated with injury.

Complications of Diabetes: The Diabetes Control and Complications Trial (DCCT)--a multi-center study of more than 1,400 people with type 1 diabetes--showed that intensive therapy to maintain blood glucose and glycosylated hemoglobin levels as close to normal as possible greatly reduced development of diabetic eye, kidney and nerve disease when compared with conventional therapy. Nearly all DCCT participants are being followed in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, an observational examination of the later-term complications of diabetes. Results of the EDIC study show that the marked reduction in the risk of progressive eye and kidney diseases in those who received intensive therapy during the DCCT persisted for at least four years, despite increases in glycosylated hemoglobin. These findings underscore the important benefits of early initiation of intensive therapy, continued for as long as possible. In related research, additional analysis of data from the United Kingdom Prospective Diabetes Study revealed associations between the development of complications and levels of both systolic blood pressure and blood sugar. These new observational data suggest that even small improvements in blood sugar and blood pressure control may prevent deaths and other complications due to diabetes.

While these important findings about diabetes management are translated into medical practice, the search continues to identify the underlying mechanism by which elevated blood glucose leads to long-term complications. Recently, it has become clear that hyperglycemia may cause damage to the endothelial cells lining the blood vessels, leading to micro- and macrovascular abnormalities. Researchers have now identified production of superoxide–an unstable form of oxygen–as a potential pathway for damage by high glucose levels. This finding may lead to more effective strategies to prevent damage to blood vessels. Identification of a protein on the surface of endothelial cells as a target for modification by glucose also represents an important step forward in the understanding of diabetes. Agents that block this modification may inhibit the development of vascular complications. Interestingly, the region of the protein modified by

glucose is present only in the human form of the protein, offering a possible molecular explanation for some of the uniquely human aspects of the disease and possibly explaining why this disease has proven so difficult to replicate completely in animal models.

Endocrine and Metabolic Diseases

Improving Management of Asymptomatic Hyperparathyroidism: Hyperparathyroidism is caused by one or more enlarged, overactive parathyroid gland(s) that produce too much parathyroid hormone (PTH). With excessive PTH, blood calcium levels rise due, in part, to transfer of calcium from the bones to the blood, which may weaken the bones and increase risk for fractures. Calcium levels may also increase in the urine, causing kidney stones. Recent studies show that many patients with mild or asymptomatic hyperparathyroidism will have a significant, rapid and sustained improvement following surgery to remove the affected parathyroid gland(s). Important developments in imaging technologies and applications have made surgery for hyperparathyroidism safer, simpler, and faster.

Correction of Membrane Lipid Imbalance in Animal Model of Cystic Fibrosis: Cystic fibrosis is a lethal genetic disease that affects the mucus glands of the body and results in thick, viscous secretions leading to serious respiratory and digestive problems. In a mouse model of the disease, a significant membrane lipid imbalance was observed in the lungs, pancreas and ileum, suggesting that membrane lipid metabolism is altered by the lack of the cystic fibrosis gene and may secondarily lead to the clinical symptoms and signs of this disease. When the mice with cystic fibrosis were fed increased amounts of certain fatty acids, the metabolic lipid imbalance was corrected and the clinical symptoms and complications of the disease were reversed. These important findings have expanded understanding of the underlying causes of cystic fibrosis and will have a profound impact on the development of new therapies.

Story of Discovery: From Bench to Bone–Basic Research Yields Osteoporosis Treatments

The bones of a person with untreated osteoporosis become weak and fragile, leading to an increased risk of fractures, which can lead to prolonged or permanent disability, even death. A comprehensive treatment program includes a focus on proper nutrition, exercise and safety issues to prevent falls that may result in fractures. In addition, medication may be prescribed that will slow or stop bone loss and increase bone density.

Although there is no cure for osteoporosis, in the past 30 years major strides have been made in its treatment. The FDA has approved several new classes of agents that help to stop bone loss and prevent further fractures. Bone cells have been shown to respond to the female hormone estrogen, which acts to slow the removal of calcium from bone. Unfortunately, estrogen, when taken alone, has been shown in some studies to slightly increase a woman's risk of developing breast and endometrial cancer. SERMs, or selective estrogen receptor modulators, were developed to maximize the beneficial effects of estrogen on bone while minimizing the adverse effects on other organs and tissues. Bisphosphonates are another class of agents that specifically target bone and act to reduce bone loss by mimicking the action of estrogen. Research on the regulation of bone development and remodeling has played a pivotal role in fueling the major scientific advances in understanding the development and progression of osteoporosis and development of more effective strategies for its treatment and prevention.

Bone is a living, growing tissue. It is made mostly of collagen, a protein that provides an elastic framework, and calcium phosphate, a mineral that adds strength and serves to harden the framework. Hormones play a major role in the regulation of bone formation and bone loss. The amount of bone mineral present in bone at any given time reflects the net difference between these two processes. Parathyroid hormone (PTH) is a key hormone responsible

for regulating the cells involved in bone formation--the osteoblasts. Paradoxically, PTH exhibits both anabolic and catabolic effects–that is, it has been shown to control the transfer of calcium both into and out of bone. A pioneering researcher isolated and purified PTH which led to the collaborative development of a novel radioimmunoassay to measure PTH levels in the blood. Using the radioimmunoassay, researchers could then study the factors governing PTH secretion. Resulting data clearly showed that changes in serum calcium, in turn, controlled PTH secretion. The isolation and purification of PTH paved the way for further studies on the synthesis of recombinant PTH and on the mechanisms of action of this hormone.

A few years later, researchers announced the successful identification, cloning and sequencing of the cellular receptor for PTH in several species, including rat, mouse and humans. Although the receptor's overall structure greatly resembled that of other trans-membrane peptide hormone receptors, it differed sufficiently so as to form a major new receptor subfamily. Once the structure was deduced, analyzing its molecular mechanism of action was then possible. Such knowledge is crucial to understanding the processes that lead to weakened bones and to the development of hormone-based therapies.

It had long been known that circulating calcium played a role in regulating the amount of PTH secreted. Yet, until recently, the exact mechanisms that permitted the cells of the parathyroid gland to secrete hormones in response to calcium levels remained unknown. Impressive studies led to the identification and cloning of a calcium-sensing receptor, defining an important step in the regulatory pathway of calcium-responsive PTH secretion. This receptor acts to "sense" extracellular levels of calcium and "signals" the parathyroid gland to regulate levels of PTH secretion. Different parts of the calcium sensing receptor structure were shown to mediate different parathyroid gland signaling pathways, explaining how secreted PTH can at times signal the osteoblast to increase bone mineral, and at other times, signal the osteoclast–a cell involved in the breakdown of bone–to reduce bone mineral. The long-term implications of this work suggested the possibility of not only designing therapeutic agents that would suppress the signaling events leading to bone loss, but of agents that would stimulate the formation of bone, such as synthetic PTH.

An understanding of the anabolic actions of hormones such as PTH led to the design of two small-scale clinical trials testing the efficacy of synthetic PTH as a treatment for osteoporosis. Results showed a beneficial effect on increasing spinal bone mineral density and preventing bone loss from the hip and total body in young women. Synthetic PTH is also proving beneficial in treating a severe form of osteoporosis caused by glucocorticoid hormones, such as prednisone, which are used to treat inflammation. An ongoing clinical study is evaluating the effect of daily administration of synthetic PTH on the risk of fractures in postmenopausal women who have glucocorticoid-induced osteoporosis and are currently receiving estrogen replacement therapy. Preliminary results show a greatly reduced risk of spine fractures and non-traumatic, non-spine fractures within one to two years of beginning therapy. Other recent research has shed light on how estrogen works to maintain bone mass by shortening the life span of the cells that are responsible for resorption of bone mineral (osteoclasts). It does so indirectly, by stimulating the production and release of a potent growth factor in bone. Without estrogen, this control is lost. The osteoclasts are no longer properly regulated, resulting in excessive bone loss.

Though no significant side effects have been attributed to PTH therapy, current treatment requires painful daily injections. Thus, the development of an oral agent that exhibits few side effects would provide a valuable treatment alternative. Some studies are under way on novel oral agents that enhance PTH secretion in animal models. These agents act through the calcium-sensing receptor, permitting PTH secretion to be regulated independently of calcium levels in the blood. Preliminary, promising results from a few studies have shown a dramatic decrease in the kind of bone turnover that results in excessive loss of bone mineral, thus suggesting additional potential therapeutic agents for the future treatment and prevention of osteoporosis and related bone disorders.

The long-term investment in studies of the underlying mechanisms of bone loss and bone remodeling, and the development of cellular and animal models to study these processes, have enabled the development of new drugs to

treat osteoporosis. These approaches have laid the foundation for understanding the mechanisms of action of these agents and for the design of safe and more effective therapies. These discoveries open exciting and promising new avenues for future exploration and provide more options for the treatment of this disease. A research imperative is to capitalize on these discoveries to develop newer, safer and more effective compounds to prevent and treat osteoporosis. With translation of these novel treatments to medical practice, it will become possible to prevent bone loss, reduce the incidence of fractures, and improve the overall quality of life for patients at risk for osteoporosis.

Digestive Diseases and Nutrition

Digestive diseases levy an enormous health burden in the United States and the world. They include a diverse number of disorders of the gastrointestinal tract, liver, gallbladder, and pancreas. Most digestive diseases are of unknown origin and have unpredictable natural history.

Liver Cells Derived from Bone Marrow in Humans: Adult stem cells have been defined by their ability to both replenish their stores by cell division and to differentiate into specialized cells, such as liver, muscle, blood and nerve cells. Mature cells, however, were previously assumed to have only the capability of producing cells of their own tissue or organ of origin. Now, research has shown that human bone marrow cells can migrate to the liver. Analyzing tissue samples obtained from women who had received a bone marrow transplant from a male donor, researchers identified liver cells containing the male Y chromosome. In another study, researchers identified the Y chromosome in liver cells in males who had received a liver transplant from a woman. These findings demonstrated that mature liver cells can be derived from circulating cells, most likely of bone marrow origin. They have major therapeutic implications for the potential use of stem cells to replace damaged tissue in the liver.

Understanding the Cause and Spread of H. pylori Infection: Worldwide, more than 50 percent of humans are chronically infected with the *H. pylori* bacterium. A portion of those infected will develop peptic ulcers, a severe form of gastritis, and/or stomach cancer. Method of transmission and frequency of infection among Americans have not been well defined. To address this problem, scientists analyzed blood samples taken from more than 7,000 individuals in the United States. Infection was diagnosed if a sample had antibodies that recognized *H. pylori*. These results were correlated with demographic factors including sex, age, race and socioeconomic status. The prevalence of *H. pylori* infection increased with age and was far higher in Mexican Americans (58 percent) and non-Hispanic blacks (51 percent) than in non-Hispanic whites (27 percent). The disparities in frequency of infection appear to be related to socioeconomic class and country of origin. Poor hygiene and crowded living conditions during childhood were associated with greater likelihood of infection. *H. pylori* was detected in vomitus and diarrheal stool, and airborne distribution was observed after episodes of vomiting. This study demonstrates how infections of this type could be spread in families, accounting for the geographical and socioeconomic-based differences in frequency of infection and providing a basis for recommendations to prevent the spread of *H. pylori* in high-risk groups.

Determinants of Recovery from Acute Hepatitis C: Hepatitis C is a common form of viral hepatitis that frequently evolves into a chronic infection that can lead to cirrhosis, end-stage liver disease and liver cancer. Researchers have not yet identified the factors of the immune response during acute hepatitis C virus (HCV) infection that lead to recovery, as opposed to chronic infection. In their search, they examined serum samples from patients infected with the same

strain of HCV during an outbreak that occurred in the late 1970s. For a large number of patients 10 to 20 years after onset of the disease, investigators were able to study long-term follow-up data, as well as samples of serum and T cells–cells used by the body in its fight against infection. They found that persons who had developed a chronic infection had high levels of antibodies against HCV (B cell, humoral immunity) but had poor HCV-specific T cell responses (cellular immunity). In contrast, patients who had acute hepatitis C in the 1970s, but then recovered, continued to have strong T cell responses to HCV 20 years later, but had low levels of antibody. Indeed, 42 percent of recovered patients had no detectable antibody to HCV 20 years after recovery, although all had tested antibody positive at 10 years post-recovery. This study indicates that T cell responses to HCV are long-lived and are perhaps a better biomarker for identifying patients with prior HCV infection and recovery. Furthermore, T cell responses appear to be responsible for clearance of virus and recovery from infection. Thus, vaccines against HCV may need to induce vigorous and long-lived T cell immunity, rather than B cell immunity. These insights into immune response will contribute significantly to the design of treatments and vaccines for HCV.

Risk of Antibiotic Treatment of E. Coli 0157:H7 Infection: A foodborne bacterium, *E. coli* 0157:H7 causes severe, sometimes life-threatening gastrointestinal infections. Approximately 15 percent of infected children also develop hemolytic uremic syndrome (HUS) which, in its most severe form, can result in kidney failure and death. Researchers have now found a strong correlation between treating infected children with antibiotics and their susceptibility to HUS. Antibiotics are not effective in combating infection by this strain of bacteria. Furthermore, it is now believed that treatment with antibiotics may trigger the release of Shiga toxin into the individual's system, putting infected children at risk for developing HUS. Therefore, it is strongly recommended that, in children with gastrointestinal infections, the source of the infection needs to be confirmed, and antibiotic therapy should *not* be initiated if the source might possibly be *E. coli* 0157:H7.

Improved Treatment for Cholera: Each year three million children worldwide die from cholera and other diarrheal diseases. These deaths are due to severe dehydration from the massive loss of salt and water associated with severe diarrhea. Currently, the standard method of treatment is rehydration therapy, which increases absorption of salt and water by the small intestine. Although this therapy corrects the dehydration caused by cholera, it does not reduce diarrhea. Researchers theorized that amylase-resistant starch, which is not absorbed by the small intestine, would provide nutrients to intestinal bacteria which, in turn, would produce more short-chain fatty acids that might stimulate increased water and electrolyte absorption. This theory was tested in a clinical trial through the administration of amylase-resistant starch in combination with rehydration therapy. The new combination therapy decreased significantly the duration and volume of diarrhea resulting from cholera infection. This approach thus provides an improved means of managing cholera throughout the world, and may also be applicable to management of other diarrheal illnesses.

Obesity: Overweight or obese individuals are at increased risk for developing type 2 diabetes, heart disease, stroke, and some forms of cancer. One possible therapeutic approach to combating weight problems is to control fat cell development. From molecular studies, researchers have

learned that mature fat cells, called adipocytes, develop from precursors known as preadipocytes. They have identified molecular factors that play critical roles in facilitating this process. Two related proteins, the transcription factors GATA-2 and GATA-3, act inside the cell nucleus, while proteins produced by *Wnt* genes signal neighboring cells. In experiments using preadipocytes in culture, inhibition of the GATA and Wnt proteins resulted in increased fat cell development. Both sets of proteins, therefore, seem to inhibit the maturation of preadipocytes into adipocytes. Strategies aimed at enhancing or mimicking these signals may become an effective treatment for obesity.

People who want to lose weight are advised to modify their diet in order to decrease the amount of food energy they consume, and to exercise in order to increase the amount of energy they expend. In this state, the body utilizes fat as an energy source. In some fat cells, the presence of "uncoupling proteins" severs the link between fat metabolism and chemical energy production, and the energy that usually drives a series of chemical reactions is instead dissipated as heat. To investigate whether uncoupling in other tissues might alter metabolism, scientists produced mice that possessed an uncoupling protein in their skeletal muscle, a major site of energy metabolism. The animals exhibited elevated rates of metabolism in both resting and active states. Compared to normal mice, uncoupled mice are leaner when maintained on a regular diet, and gain less weight when placed on a high-fat diet. This research suggests that uncoupling and dissipating fat energy as heat might represent a viable strategy for preventing or treating obesity.

Recent research advances in the molecular biology of obesity reflect progress achieved through a very substantial NIDDK research initiative to address this serious public health problem. Included in this effort is an intensive program of basic and clinical research on obesity and eating disorders, support of four Obesity-Nutrition Research Centers and eight Clinical Nutrition Research Centers, establishment of a National Task Force on the Prevention and Treatment of Obesity, and a Weight Control Information Network to disseminate science-based informational messages about obesity. The NIDDK has two major obesity-related research initiatives currently under way. The first is a multi-center clinical trial, the Action for Health in Diabetes (Look AHEAD) study. The second is a trans-NIH prevention activity focused on successful pilot studies of innovative approaches to prevention of obesity in high-risk populations, such as minority populations and women. In the coming year, the Institute will convene a meeting of grantees who received funding through the pilot prevention research initiative so that they can share the preliminary results of their studies and identify possible opportunities for full-scale obesity prevention studies. Another objective of the NIDDK's obesity research initiative is to address the contributory role that the increase in childhood obesity is believed to play in the alarming increase of type 2 diabetes in children. Highly relevant to the issue of obesity as a risk factor for type 2 diabetes is a new trans-NIH research initiative to investigate the relationship between physical activity and obesity. Studies will be encouraged to more accurately assess physical activity and energy balance, and to develop and test interventions that incorporate physical activity for obesity prevention or treatment related to chronic diseases such as type 2 diabetes. The NIDDK has also increased its efforts to translate obesity research findings to the health care community and the general public through its Weight

Control Information Network, and also participates in joint efforts with the *Obesity Education Initiative* of the National Heart, Lung, and Blood Institute. These joint efforts resulted in the publication of "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults."

Story of Discovery: Solving the Puzzle of Inflammatory Bowel Disease

The inflammatory bowel diseases (IBD) known as Crohn's disease and ulcerative colitis affect nearly one million Americans. Typical symptoms of IBD include abdominal pain, fever, watery or bloody diarrhea, weight loss, and fatigue. Both forms of IBD are chronic illnesses that typically affect children and young adults and exact a major impact on their health and quality of life. Traditional therapy for IBD has consisted of immunosuppressive and anti-inflammatory drugs, antibiotics, and drugs to relieve the pain, fever, and other overt symptoms. Unfortunately, about one third of patients do not respond to medical treatment, and--in patients who do respond--remission is usually followed by relapse. Many patients ultimately require one or more surgeries to alleviate their symptoms.

Research is yielding new clues about the common final manifestation of IBD: chronic inflammation of the intestinal tract. The inflammatory process is facilitated in part by the production of cytokines, proteins released by cells to alert the body to the presence of a foreign substance. Cytokines may either promote or inhibit inflammation; but under normal conditions, a balance exists between signals that promote inflammation and those that inhibit it. In patients who suffer from IBD, however, this balance is perturbed and pro-inflammatory signals predominate in the intestinal tract, leading to chronic inflammation and resultant tissue damage. While the trigger for this disturbance is unknown, it seems to arise from an abnormal reaction by the immune system to the bacteria normally present within the gut. A likely explanation for this aberrant immune response is that susceptible individuals inherit a genetic predisposition to IBD and possess an immune system unable to distinguish between benign and threatening stimuli.

Animal models of IBD have revealed new insights into the origins of IBD. For example, mice engineered to overproduce TNF-alpha, a potent pro-inflammatory cytokine, exhibit severe intestinal inflammation that closely resembles human Crohn's disease. Mice lacking IL-10, an anti-inflammatory cytokine, also develop widespread intestinal inflammation. Together, these findings indicate that disequilibrium in the balance between the levels of pro- and anti-inflammatory signals, resulting from either increased production of factors that promote inflammation or the absence of factors that inhibit it, can give rise to conditions that closely resemble IBD. These studies support the hypothesis that IBD may arise from an inappropriate immune response to otherwise benign environmental factors. These insights are currently being translated into novel therapies that target the molecular mediators of inflammation. One strategy involves targeting TNF-alpha, perhaps the prototypic pro-inflammatory cytokine. In active Crohn's disease, a single injection of infliximab, an antibody that inactivates TNF-alpha, promotes a clinical response in two-thirds of patients and remission in approximately one-third. Infliximab (Remicade®) was recently licensed in the U.S. and Europe for treating Crohn's disease. IL-10 has also been investigated as a potential therapy. In a small trial, disease activity was lower and remission rates were twice as high in Crohn's patients who received IL-10 for three weeks compared to those who did not.

Unexpected insights into the molecular causes of IBD have come from recent studies of PPAR-gamma. The PPAR-gamma protein is a member of a family of proteins, known as transcription factors, which regulate which genes are turned on or off within a given cell. Studies have shown that the PPAR-gamma gene is expressed in cells of the large intestine where it can inhibit the production of pro-inflammatory cytokines. This discovery has led to the consideration of agents that activate PPAR-gamma, and thereby reduce the levels of pro-inflammatory cytokines, as possible therapies for IBD A pilot clinical trial, supported by NIDDK, is now under way to investigate this possibility.

Future improvements in treatment of IBD are likely to come from the identification of the genetic lesions that initially give rise to the disease. To identify genes that may be involved in a given disorder, scientists analyze DNA from genetically similar people, such as large families or members of relatively homogeneous ethnic groups, and look for a correlation between specific chromosomal segments and the occurrence of the disease. Using this approach, researchers have noted several genetic regions that seem to correlate with the development of IBD. The identification of multiple genetic loci on different chromosomes–some for Crohn's disease, some for ulcerative colitis, and others for both–suggests that there is unlikely to be a single underlying defect responsible for all forms of IBD. Along with determining genetic predisposition, researchers are conducting important work to investigate the possibility that combinations of agents–each targeting a different component of the immune response or a different facet of the disease–will prove more effective in the management of IBD than any single therapy. Taken together, the insights researchers are accumulating about IBD offer great hope of solving this extremely puzzling set of diseases.

Kidney, Urologic, and Hematologic Diseases

Virus Can Cause Kidney Inflammation: Kidney inflammation most often occurs from known causes, but can arise from unknown causes as well. A recent clinical report identified Epstein-Barr virus (EBV) in the kidneys, but not in the other tissues, of patients with chronic kidney inflammation not attributable to known causes. The virus was localized to a specific part of the kidney's functional unit called the proximal tubule of the nephron. This report is the first identification of EBV in this location, suggesting that infection with this virus may induce a marked immune response and associated inflammation that result in structural damage to the kidney. While infection with EBV rarely affects kidney function significantly, this study suggests that examination of a kidney biopsy for this virus would be an important diagnostic measure when physicians have ruled out other causes of kidney disease as being responsible for some loss of kidney function.

Cause of Kidney Failure in Diabetic Mice: Diabetes is the most common cause of end-stage kidney disease. Diabetes patients account for 42 percent of those currently receiving dialysis or kidney transplantation through the Medicare End-Stage Renal Disease Program. Researchers report that, in mice with diabetes, kidney failure is caused by overproduction of a protein called transforming growth factor beta. This protein causes scar tissue inside the kidneys, which eventually interferes with kidney function. Key to this finding is that the mice do not develop kidney failure when the protein is neutralized with an antibody against it. This is the first proof-of-concept study showing that transforming growth factor beta may cause end-stage kidney disease in diabetes. Armed with this knowledge, researchers are now better positioned to pursue drug treatments for diabetic kidney failure--targeted to inhibition of this protein. This advance is highly relevant to both type 1 and type 2 diabetes, because kidney complications occur in both forms of the disease.

Story of Discovery: Why the Kidney Sometimes Leaks Protein–Studies of Cells with Feet

Normal kidneys work very efficiently to cleanse the blood of waste products and retain normal blood constituents–water, salts, and blood proteins. The first step in this process is filtration of the blood plasma by the renal glomerulus, a complex structure consisting of a tiny ball of delicate capillaries surrounded by special cells called *podocytes*. The human kidney has a million of these tiny filters. Massive quantities of fluid are filtered from

the blood by the glomeruli, about one hundred and eighty liters per day, but very little protein escapes. Blood proteins do not leak out because the filtration properties of the glomerulus result in retention of large molecules such as albumin and other proteins. The podocyte–the word means cell with feet–is a critical component of this filter. New evidence establishes that it plays the major role in synthesizing the scaffold that lets fluid through and holds back blood proteins; it is the key to maintaining the integrity of the filter.

Physicians have long been aware that leakage of protein into the urine (proteinuria) is an important early sign of kidney disease, but the significance of even low levels of proteinuria as a risk factor for eventual kidney failure has only recently been appreciated. In the last few years, several large clinical trials have examined the progression of kidney dysfunction to kidney failure; it has been found that patients with small amounts of protein in the urine are much more likely to progress to kidney failure than other patients who have equally severe kidney dysfunction but who do not have protein in the urine. In patients with diabetes, the earliest warning for the presence of kidney involvement is the appearance of small amounts of albumin in the urine. Recent studies show that reduction in the amount of albumin in the urine is associated with stabilization of disease, and increases in albumin and other urine proteins are linked to development of kidney failure.

Another important condition characterized by proteinuria is nephrotic syndrome. The end result of a variety of diseases, this condition is characterized by massive losses of blood proteins into the urine. Loss of large amounts of protein in the urine causes a variety of disturbances in body function, including retention of salt and water, high blood pressure and high cholesterol. One of the most common forms of nephrotic syndrome occurs in children. In some rare cases, it runs in families. Currently, treatment of nephrotic syndrome focuses on identifying the underlying cause, if possible, and reducing high cholesterol, blood pressure, and proteinuria through diet, medications, or both. One group of blood pressure medications, known as ACE inhibitors, protects the kidneys of diabetic patients. These drugs are sometimes helpful for reducing proteinuria in nephrotic syndrome, but in many cases proteinuria is resistant to treatment. All of these observations underscore the importance of understanding the glomerular filter and learning what holds back proteins in the glomerulus and what causes leakiness.

Over several decades, basic research on the kidney glomerulus has yielded a clear description of the filtration barrier. The filter is composed of three layers: the cells lining the capillaries (endothelial cells), the podocytes (the cells with feet) and the glomerular basement membrane, a collagenous gel that separates the two cell layers. Stretching between the "feet" of the podocytes is the "slit diaphragm," the principal filtration barrier to large blood proteins.

The first genetic defect established to cause leakage of proteins into the urine was in the collagen molecules that make up the glomerular basement membrane. Defects in this form of collagen cause Alport's syndrome, a disorder in which protein leaks into the urine and increase the likelihood of developing kidney failure. Kidney biopsies from patients with Alport's syndrome show very thin glomerular basement membranes. In most conditions involving protein in the urine, however, the glomerular basement membranes appear structurally normal.

Increasingly, research interest has focused on the podocyte and on understanding the special molecules that the podocyte uses to form the slit diaphragm and maintain the filtration barrier. In the past three years, there has been a rapid series of important discoveries in understanding the molecular basis of podocyte function–and malfunction. These insights have emerged primarily from the application of genetic approaches to either man or mouse, but they have been helped by decades of studies in rats and insights from the genome of the roundworm.

The first of these observations occurred in 1998, when scientists found the gene mutated in a rare type of hereditary nephrotic syndrome found in Finnish families. The gene's protein product, called nephrin, was found to be expressed only in the podocyte and to be a major component of the slit diaphragm filtration barrier. In 1999, a second group of investigators discovered, unexpectedly, that massive proteinuria and kidney failure developed in mice that were altered genetically to lack a protein named CD2 adaptor protein (CD2AP), a protein not previously known to be important in kidney function. In fact, prior to these studies, CD2AP was thought to function only as a T lymphocyte protein and part of the immune system. The researchers found that, in fact, CD2AP interacts with

nephrin in the slit diaphragm, and suggested that CD2AP may serve to anchor nephrin to the podocyte. Then, in March 2000, scientists reported the discovery–again using genetic approaches–of a third protein, named -actinin-4, that is produced by a gene located close to the nephrin gene. Mutations in this gene cause a kidney disease called focal sclerosis that leads to nephrotic syndrome and kidney failure in adulthood. The investigators showed that mutant -actinin-4 actually binds more strongly to a protein in the podocyte that helps maintain the shape of the cell's foot processes than does -actinin-4 from non-affected individuals. The mutant -actinin-4 also is produced at higher levels in podocytes. They speculate that altered -actinin-4 may act in a dominant fashion to alter podocyte foot shape, thereby altering the structure of the slit diaphragm and glomerular function, resulting in slow accumulation of kidney damage.

Following these observations in close succession was another report in April 2000, of a fourth gene which, when mutated, causes proteinuria. The gene produces a membrane protein, named podocin, and again, it is exclusively expressed in the podocyte. It was found to be defective in 13 families with a form of nephrotic syndrome that presents in infancy and rapidly leads to kidney failure. While the precise function of podocin is not yet known, it is very similar to a protein called MEC-2 found in the roundworm, *C. elegans*. MEC-2 functions to link stretch-sensitive ion channels on the cell surface with internal skeletal structures of the cell. Thus, these investigators suggested that podocin may be important for cell-surface interactions critical in maintaining the shape of podocyte foot processes. This research is an example of how detailed knowledge of the genome of a simpler, non-mammalian model system has helped to accelerate the pace of human disease research. In the case of *C. elegans*, investigators will be able to perform studies of the podocin-like protein to define its interactions with other proteins. This information will bear directly on the study of the filtration barrier in humans.

Studies of these four proteins–nephrin, CD2AP, -actinin, and podocin–are revolutionizing fundamental knowledge of the molecular mechanisms of glomerular filtration. As abnormal function of the filtration barrier is a major complication in most clinically important kidney diseases, such as hypertensive nephropathy and diabetic kidney disease, further studies of these proteins hold great promise to suggest new strategies for treatment and prevention.

Urinary Tract Infections--Identification of Molecular Mechanisms of Infection: Acute urinary tract infections (UTIs) are among the most common infectious diseases. The bacterium *Escherichia coli* (*E. coli*) is the primary causative agent of UTIs. Molecular interactions that occur between the infecting, pathogenic (disease-causing) organism and the host cells of the bladder are among the earliest events in these infections. Colonization–the ability of pathogenic bacteria to gain a foothold in host tissues–is usually mediated by substances called adhesins, which are found on the surface of the infecting microbe. The adhesins are responsible for recognizing and binding to specific receptor moieties of host cells. In many organisms, the adhesins are assembled into hair-like appendages called pili that extend out from the bacterial surface. In mice, it has been shown that a particular adhesin, called FimH, is required for *E. coli* colonization that produces disease. Several scientific reports in the last year increased knowledge of the molecular mechanisms of UTIs. Extending previous studies in mice and cell culture, investigators found that monkeys vaccinated with FimH produced antibodies to it, and did not develop infections when challenged, suggesting that the FimH vaccine induced protective immunity. A second study found that FimH not only is critical for adherence of *E. coli* to bladder cells, but also for the actual invasion of the bacteria into the cells. It appears that FimH binding begins a cascade of events in the host cell membrane that results in internalization of the bacterium. A third study showed that a protein that is complexed with FimH–called a chaperone protein--is necessary for proper folding and function of the FimH protein itself. Interestingly, a small amino acid segment of the chaperone could perform the folding function of the full chaperone. Another study examined *E. coli* infection involving FimH in bone marrow-derived mast cells. Mast cells are a type of white blood cell that store and release a

variety of inflammatory mediators, such as histamine. The uptake of the disease-producing *E. coli* was dependent on specialized pocket-like areas of the mast cell called caveolae–meaning "little caves"–that contain a unique type of protein. The *E. coli* with FimH attach to multiple caveolae on the mast cell, forming massive caveolae-like vesicles that internalize the bacteria. Compounds that disrupt caveolae block bacterial uptake by the cells and may have therapeutic potential. Collectively, these studies provide insights into the molecular mechanisms of disease-producing *E. coli* infection that will be critical in developing effective, long-lasting therapies and preventive strategies for UTIs.

Genetic Correction of Sickle Cell Disease: Hemoglobin is the iron-protein compound in red blood cells that gives blood its red color and transports oxygen, carbon dioxide, and nitric oxide throughout the body. So-called "fetal" hemoglobin is the main hemoglobin present in the developing fetus during the last six months of pregnancy. A few weeks before birth, the baby starts to make increasing amounts of "adult" hemoglobin, which is better suited to the oxygen transport needs after birth and throughout adult life. After birth, the baby makes less fetal hemoglobin and more adult hemoglobin. Fetal hemoglobin does not turn into adult hemoglobin–they are completely different hemoglobins. A genetic abnormality in the adult form of hemoglobin causes red blood cells to take on a "sickling" shape that is characteristic of sickle cell disease. Patients who also produce the fetal form of hemoglobin generally have reduced clinical evidence of the disease, such as low red blood cell count. When researchers mated mice having experimental sickle cell disease with those that express the human fetal hemoglobin gene, the offspring had a less severe form of the disease. Direct therapeutic effects of fetal hemoglobin were demonstrated. The mouse models may now be used for quantitative assessment of the contribution of fetal hemoglobin to the inhibition of sickling and for developing new genetic approaches for sickle cell disease.

Highlights of Planned Activities

Diabetes, Endocrinology, and Metabolic Diseases: In collaboration with other NIH institutes and centers, the NIDDK plans to build upon earlier research initiatives such as: prevention and treatment of type 2 diabetes in children and adolescents, particularly among minority populations; genetics of type 1 and type 2 diabetes; the diabetes genome anatomy program; the clinical trial network for type 1 diabetes; immune tolerance in type 1 diabetes; and further studies to improve methods for islet transplantation as a potential cure for type 1 diabetes. In response to scientific recommendations from the community, the NIDDK will strive to intensify research to accumulate new knowledge about the effect of low blood glucose levels on the brain, especially in young children. In addition, the NIDDK will continue to bolster its diabetes research portfolio with efforts to harness new and improved technologies for imaging the beta cell. Improved imaging technology may prove useful for earlier detection of diabetes, studies of the mechanisms of disease development, and monitoring the success of treatment. The NIDDK will also continue to support studies on mouse models of diabetes and its complications.

Digestive Diseases and Nutrition: The NIDDK will pursue new insights into promising areas of research on inflammatory bowel disease, as well as strategies for establishing a genetics consortium and a clinical network for studies of both pediatric and adult forms of the disease. In a collaborative effort, the National Cancer Institute and the NIDDK will identify areas for intensive investigation of

the disease process in Barrett's esophagus and its potential to lead to esophageal cancer. In obesity research, the NIDDK will build upon its prevention research initiative by focusing on the development of innovative approaches to decreasing the prevalence of obesity through societal and environmental interventions. Recent scientific recommendations concerning new directions in drug-induced liver injury will lead spur expanded research on the mechanisms involved in specific agents that are toxic to the liver. A recently-convened NIH workshop on adult-to-adult living donor liver transplantation will be the impetus for new studies on this procedure, including ethical, technical, medical and basic research issues. It may also lead to recommendations for a database to analyze the consequences of this surgery on the liver function, health, and quality of life of living donors.

Kidney, Urologic, and Hematologic Diseases: A clinical trial consortium will pilot interventional studies to examine whether protein and energy supplementation can improve nutritional indices, and ultimately mortality, in malnourished dialysis patients, and whether anti-inflammatory interventions diminish the deterioration seen in this state. Another planned research initiative is to determine whether immunosuppressive agents, such as cyclosporine, may be beneficial in arresting progression of focal sclerosis in children. The NIDDK will also establish a multi-center prospective cohort study of patients with inadequate kidney function to determine factors associated with rapid decline in renal function and to identify risk factors for cardiovascular disease. The NIDDK will continue to strengthen its PKD research program through enhanced efforts to develop state-of-the-art imaging methods for accurate and reproducible markers of progression of kidney for use in clinical trials. The Institute is also planning a multi-center interventional clinical trial to assess the best strategy for reducing morbidity and mortality in PKD. To reduce the morbidity and mortality of kidney disease through educational messages, the NIDDK is undertaking a new National Kidney Disease Education Program. In urologic diseases, a trial network is planned to assess the effectiveness of measures to reduce urinary tract infections in diabetic women and to determine whether such measures improve control of blood glucose in these patients. With respect to benign prostatic hyperplasia (BPH), the NIDDK is planning a research initiative on alternative and complementary therapies for symptomatic disease. This activity will develop a collaborative research group to assess the efficacy of widely used alternative and complementary strategies for treatment of BPH and to compare these agents with FDA-approved drugs. To increase understanding of chronic pelvic pain of the bladder and interstitial cystitis as a foundation for new treatment approaches, the Institute is undertaking a multi-institution, collaborative epidemiological study to determine the prevalence, incidence, risk factors, quality of life and functional status, and health resource utilization of patients. A new effort to develop a compendium of data on urologic diseases in America will assist in delineating the changes in the epidemiology, health economic impact, and practice patterns for urologic diseases, analyzed retrospectively over a ten-year period.

Other Areas of Interest

In FY 2002, the NIDDK will continue to support a robust program of research centers in its extramural operating divisions. These include research centers focused on: diabetes; diabetes/ endocrinology; cystic fibrosis; kidney and urologic diseases; digestive diseases; obesity/ nutrition; clinical nutrition; and molecular hematology.

The NIDDK also will continue vigorous support of its clinical trials programs. The Diabetes Prevention Program (DPP) is an ongoing multi-center clinical trial to determine whether lifestyle and pharmacologic interventions can prevent or delay the onset of type 2 diabetes in people at risk for the disease. In type 1 diabetes, the Diabetes Prevention Trial (DPT-1) is investigating whether early intervention using antigen-based therapies (injection or oral insulin) in at-risk nondiabetic relatives of individuals with type 1 diabetes can delay the development of the disease.

A multi-center, randomized clinical trial called Action for Health in Diabetes (Look AHEAD) will address two primary research questions. The first is: Do interventions designed to produce sustained weight loss in obese individuals with type 2 diabetes improve health? The second is: How do the benefits and risks of such interventions compare with those associated with the treatment of obesity-related co-morbid conditions in the absence of weight loss intervention? A research solicitation was issued to seek additional basic, clinical, and behavioral research studies that are consistent with the aims of the Look AHEAD trial and can be efficiently undertaken in the same patient population.

The NIDDK has launched an important new clinical trial, "Hepatitis C Antiviral Long-Term Treatment to Prevent Cirrhosis (HALT-C)." This long-term, multi-center clinical trial should help to determine whether progression of hepatitis C can be halted or modified in individuals who previously were virologic non-responders to treatment. Patients will initially receive a combination of long-acting (PEGylated) interferon and ribavirin. Those who continue as non-responders, presumed to be about 80 percent of the initial treatment group, will then be randomized to receive either PEGylated interferon alone or a placebo. To maximize the knowledge that can be gained from this trial, the Institute has also sought the development of ancillary studies that will be co-funded with other NIH components who share a mutual research interest in hepatitis C.

Recently, the African American Study of Kidney Disease and Hypertension (AASK) determined that individuals with kidney disease and protein in their urine can be treated more effectively with either an angiotensin-converting enzyme inhibitor or a beta blocker than with a calcium channel blocker. Because these findings are so important for medical practice, the NIDDK concluded this part of the study earlier than planned so that the results could be made immediately available to physicians and patients. The Family Investigation of Nephropathy and Diabetes (FIND)study is investigating genes associated with the presence and severity of diabetic kidney disease in Caucasian, African American, Hispanic, and Native American populations across the U.S. In the Hemodialysis (HEMO) trial, researchers are determining the effects of different hemodialysis regimens on morbidity and mortality in end- stage renal disease patients. In urologic research, the clinical trial on Medical Therapy of Prostate Symptoms (MTOPS) is assessing the effect of drug therapy on prostate growth to determine whether it is possible to postpone or prevent the need for

surgery or additional treatment. A Collaborative Research Network is developing and following a cohort of patients who meet a standard definition of chronic prostatitis, which should be useful in resolving questions regarding clinical characteristics and natural history.

AIDS

In recent years, HIV treatment has been revolutionized by the advent of highly active anti-retroviral therapy (HAART). Despite the benefits of new anti-HIV therapies, a variety of metabolic alterations have been attributed to long-term use of protease inhibitors and possibly to other classes of anti-retroviral agents as well. HAART may lead to a number of metabolic complications -- including changes in lipid levels, the development of insulin resistance, and abnormal distribution of body fat -- all of which are major risk factors for the subsequent development of other serious diseases, including diabetes and cardiovascular disease.

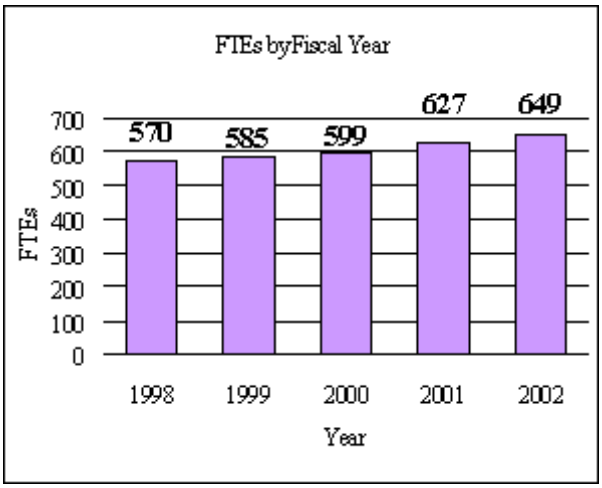
NIDDK investigators have made significant contributions to our understanding of the pathways regulating food intake, energy balance, and body composition in individuals living with AIDS. These advances are important because the metabolic complications of HAART have important public health implications. Of particular concern for many patients on HAART has been the problem of body fat redistribution. Known as lipodystrophy, this process is characterized by increased deposition of fat in the abdomen and trunk and loss of it in the face and limbs. Lipodystrophy represents a two-fold health problem because accumulation of fat in the abdomen increases the probability of developing diabetes and cardiovascular disease; furthermore, distress over the disfiguring physical changes causes many patients to stop taking antiviral medications that are holding their HIV in check. NIDDK is pursuing investigations into the epidemiology, genetics and mechanisms that underlie the process of fat redistribution and the development of insulin resistance and other complications in individuals on HAART.

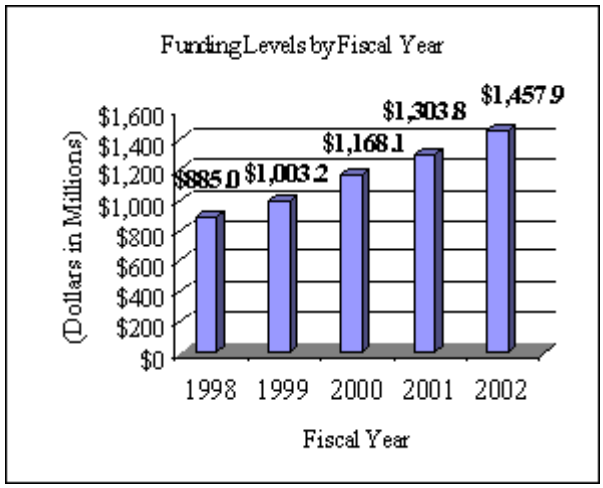
NIDDK is also interested in understanding organ-specific complications of AIDS, including HIV-associated nephropathy and the association of HIV and hepatitis C. In addition, NIDDK funds other AIDS-related projects, including the role of mucosal immunity in AIDS and opportunistic infection, research into HIV replication, the biology of the HIV “receptor” on cells, and the mechanism of the sexual transmission of HIV.

Budget Policy

The Fiscal Year 2002 budget request for the NIDDK is $1,457,915,000, including AIDS, an increase of $154,098,000 and 11.1 percent over the FY 2001 level, and $289,609,000 and 24.7 percent over FY 2000.

A five year history of FTEs and Funding Levels for NIDDK are shown in the graphs below:





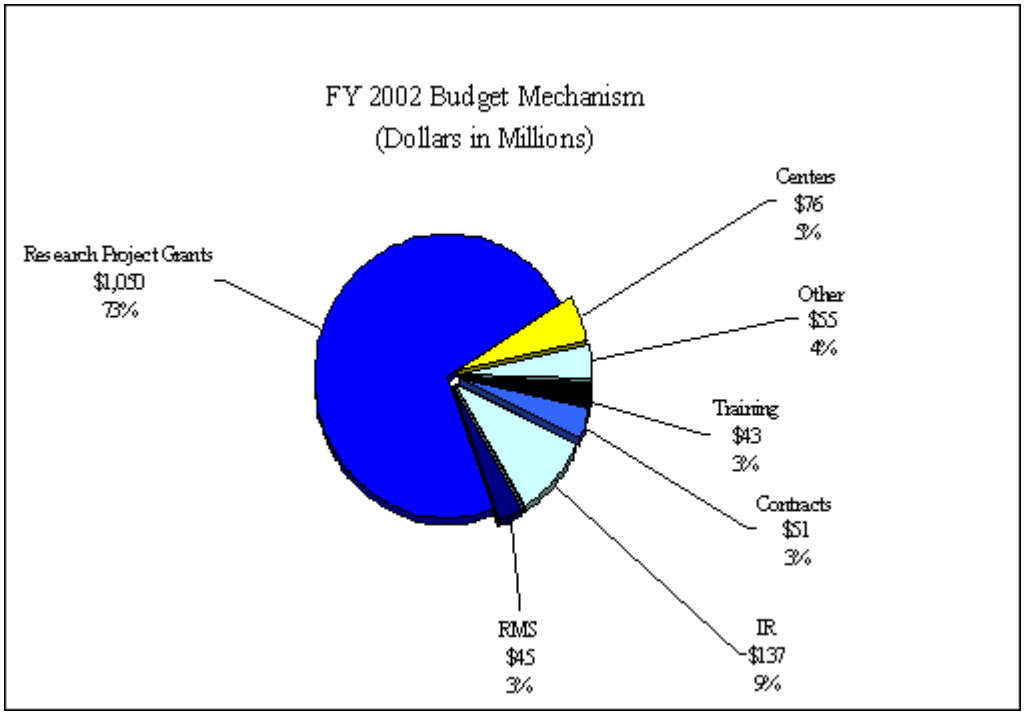
One of NIH's highest priorities is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. The Fiscal Year 2002 request provides average cost increases for competing RPGs equal to the Biomedical Research and Development Price Index (BRDPI), estimated at 4.3 percent. Noncompeting RPGs will receive increases of 3 percent on average for recurring direct costs. In FY 2002, total RPGs funded will be 3,140 awards, an increase of 161 awards over the FY 2001 Estimate, the highest annual total ever awarded.

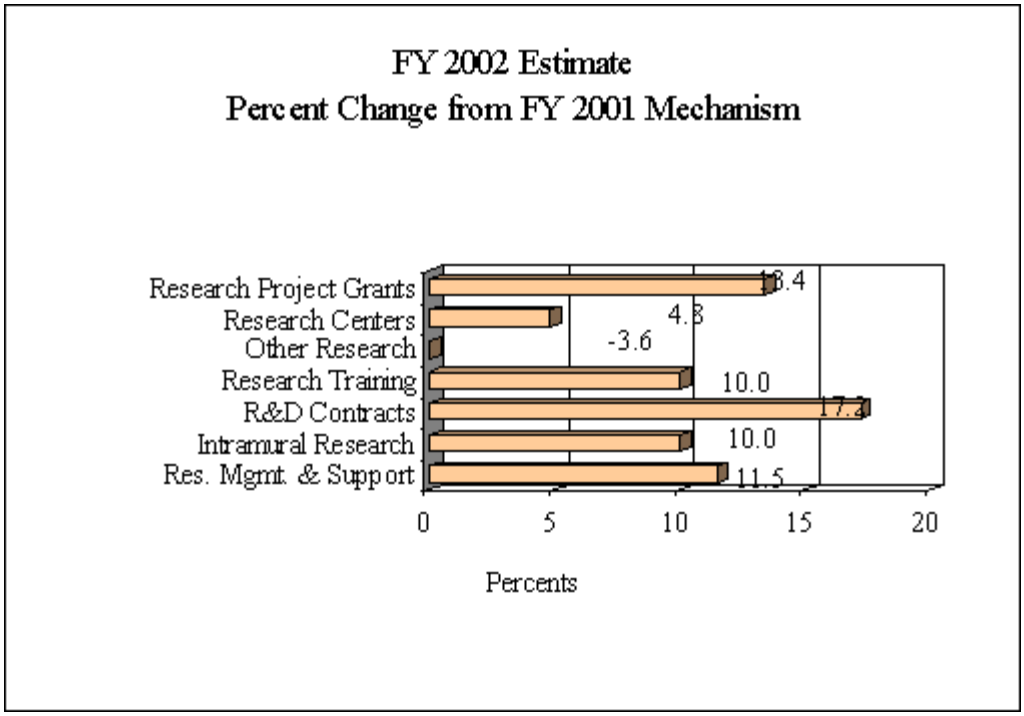
Promises for advancement in medical research are dependent on a continuing supply of new investigators with new ideas. In the Fiscal Year 2002 request, NIDDK will support 872 pre- and postdoctoral trainees in full-time training positions. An increase of 10 percent over Fiscal Year 2001 levels is provided for stipends and training-related expenses (e.g., health insurance, research supplies and equipment, and travel to scientific meetings).

The Fiscal Year 2002 request includes funding for 73 research centers, 429 other research grants, including 12 new clinical career awards, and 77 R&D contracts.

The Research Management and Support increase for the NIDDK will support an increase of 22 scientific program management staff and a number of increased costs for research initiatives which are incorporated into the grant and contract portions of the request. These include major new clinical trial networks, clinical research databases, epidemiologic studies following completion of major clinical trials, and programs for specialized resources in support of research. The Institute has taken on new renovation and lease costs as a result of the move of most of the program

management staff to a building off the NIH campus. This has also necessitated the expansion of our technical support staff and information technology resources. In FY 2002, the NIDDK will be establishing an important new Public Health Education effort, the National Kidney Disease Education Program, and will work to meet the expanding demand on its other public health education programs. The mechanism distribution by dollars and percent change are displayed below:





NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Budget Mechanism

MECHANISM	FY 2000 Actual		FY 2001 Estimate		FY 2002 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	2,017	$595,663,000	2,072	$659,788,000	2,108	$736,500,000
Administrative supplements	(211)	12,673,000	(150)	10,500,000	(150)	10,500,000
Competing:						
Renewal	223	73,526,000	248	84,386,000	280	99,279,000
New	456	125,006,000	503	143,071,000	568	168,320,000
Supplements	5	385,000	5	400,000	5	400,000
Subtotal, competing	684	198,917,000	756	227,857,000	853	267,999,000
Subtotal, RPGs	2,701	807,253,000	2828	898,145,000	2961	1,014,999,000
SBIR/STTR	126	24,770,000	151	27,972,000	179	35,227,000
Subtotal, RPGs	2,827	832,023,000	2979	926,117,000	3140	1,050,226,000
Research Centers:						
Specialized/comprehensive	68	66,428,000	71	72,375,000	73	75,875,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	0	0	0	0	0
Comparative medicine	0	0	0	0	0	0
Research Centers in Minority Instituti	0	0	0	0	0	0
Subtotal, Centers	68	66,428,000	71	72,375,000	73	75,875,000
Other Research:						
Research careers	277	32,050,000	324	39,163,000	371	43,766,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	0	0	0	0	0	0
Biomedical research support	0	0	0	0	0	0
Minority biomedical research support	0	2,629,000	0	3,000,000	0	3,354,000
Other	43	12,699,000	72	15,149,000	58	8,134,000
Subtotal, Other Research	320	47,378,000	396	57,312,000	429	55,254,000
Total Research Grants	3,215	945,829,000	3446	1,055,804,000	3642	1,181,355,000
Training:	FTTPs		FTTPs		FTTPs	
Individual awards	142	5,420,000	142	5,830,000	142	6,413,000
Institutional awards	730	31,130,000	730	33,331,000	730	36,664,000
Total, Training	872	36,550,000	872	39,161,000	872	43,077,000
Research & development contracts	58	35,959,000	66	43,503,000	77	50,993,000
(SBIR/STTR)	(5)	(767,000)	(8)	(2,000)	(8)	(2,000)
	FTEs		FTEs		FTEs	
Intramural research	418	115,218,000	421	124,903,000	436	137,393,000
Research management and support	181	34,750,000	206	40,446,000	213	45,097,000
Cancer prevention & control	0	0	0	0	0	0
Construction		0		0		0
Total, NIDDK	599	1,168,306,000	627	1,303,817,000	649	1,457,915,000
(Clinical Trials)		(97,550,000)		(111,000,000)		(124,000,000)

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 2000 Actual		FY 2001 Estimate		FY 2002 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:								
Division of Diabetes, Endocrinology and Metabolic Diseases		$455,235		$508,857		$570,115		$61,258
Division of Digestive Diseases and Nutrition		274,328		306,722		343,599		36,877
Division of Kidney, Urologic and Hematologic Diseases		288,775		322,889		361,711		38,822
Subtotal, Extramural research		1,018,338		1,138,468		1,275,425		136,957
Intramural research	418	115,218	421	124,903	436	137,393	15	12,490
Research management and	181	34,750	206	40,446	213	45,097	7	4,651
Total	599	1,168,306	627	1,303,817	649	1,457,915	22	154,098

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Summary of Changes

2001 Estimated budget authority				$1,303,817,000
2002 Estimated budget authority				1,457,915,000
Net change				154,098,000
	2001 Current Estimate Base		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$46,748,000		$672,000
b. Annualization of January 2001 pay increase		46,748,000		432,000
c. January 2002 pay increase		46,748,000		1,292,000
d. One extra day of pay		46,748,000		179,000
e. Payment for centrally furnished services		24,114,000		2,411,000
f. Increased cost of laboratory supplies, materials, and other expenses		54,041,000		2,360,000
Subtotal				7,346,000
2. Research Management and Support:				
a. Within grade increase		19,553,000		281,000
b. Annualization of January 2001 pay increase		19,553,000		181,000
c. January 2002 pay increase		19,553,000		540,000
d. One extra day of pay		19,553,000		75,000
e. Payment for centrally furnished services		4,552,000		455,000
f. Increased cost of laboratory supplies, materials, and other expenses		16,341,000		701,000
Subtotal				2,233,000
Subtotal, Built-in				9,579,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Summary of Changes--continued

CHANGES	2001 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	2072	670,288,000	36	76,712,000
b. Competing	756	227,857,000	97	40,142,000
c. SBIR/STTR	151	27,972,000	28	7,255,000
Total	2979	926,117,000	161	124,109,000
2. Centers	71	72,375,000	2	3,500,000
3. Other research	396	57,312,000	33	(2,058,000)
4. Research training	872	39,161,000	0	3,916,000
5. Research and development contracts	66	43,503,000	11	7,490,000
Subtotal, extramural				136,957,000
	FTEs		FTEs	
6. Intramural research	421	124,903,000	15	5,144,000
7. Research management and support	206	40,446,000	7	2,418,000
Subtotal, program		1,303,817,000		144,519,000
Total changes	627		22	154,098,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases
Budget Authority by Object

	FY 2001 Estimate	FY 2002 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	627	649	22
Full-time equivalent of overtime and holiday hours	4	4	0
Average ES salary	$136,710	$143,546	$6,836
Average GM/GS grade	11.0	11.0	0.0
Average GM/GS salary	$63,154	$66,312	$3,158
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	$71,323	$74,889	$3,566
Average salary of ungraded positions	$79,403	$82,182	$2,779

	OBJECT CLASSES	FY 2001 Estimate	FY 2002 Estimate	Increase or Decrease
	Personnel Compensation:			
11.1	Full-Time Permanent	$28,779,000	$30,500,000	$1,721,000
11.3	Other than Full-Time Permanent	12,500,000	13,250,000	750,000
11.5	Other Personnel Compensation	1,820,000	1,925,000	105,000
11.8	Special Personnel Services Payments	11,477,000	12,170,000	693,000
11.9	**Total Personnel Compensation**	**54,576,000**	**57,845,000**	**3,269,000**
12.0	Personnel Benefits	11,700,000	12,400,000	700,000
13.0	Benefits for Former Personnel	4,000	4,000	0
	Subtotal, Pay Costs	**66,280,000**	**70,249,000**	**3,969,000**
21.0	Travel & Transportation of Persons	2,109,000	2,300,000	191,000
22.0	Transportation of Things	360,000	395,000	35,000
23.1	Rental Payments to GSA	10,000	11,000	1,000
23.2	Rental Payments to Others	902,000	1,000,000	98,000
23.3	Communications, Utilities & Miscellaneous Charges	1,640,000	1,800,000	160,000
24.0	Printing & Reproduction	900,000	980,000	80,000
25.1	Consulting Services	1,682,000	1,867,000	185,000
25.2	Other Services	3,692,000	4,098,000	406,000
25.3	Purchase of Goods & Services from Government Accounts	71,818,000	79,347,000	7,529,000
25.4	Operation & Maintenance of Facilities	5,184,000	5,704,000	520,000
25.5	Research & Development Contracts	43,503,000	50,990,000	7,487,000
25.6	Medical Care	1,106,000	1,227,000	121,000
25.7	Operation & Maintenance of Equipmen	1,696,000	1,883,000	187,000
25.8	Subsistence & Support of Persons	0	0	0
25.0	**Subtotal, Other Contractual Services**	**128,681,000**	**145,116,000**	**16,435,000**
26.0	Supplies & Materials	14,318,000	15,893,000	1,575,000
31.0	Equipment	7,898,000	8,767,000	869,000
32.0	Land and Structures	0	0	0
33.0	Investments & Loans	0	0	0
41.0	Grants, Subsidies & Contributions	1,080,719,000	1,211,404,000	130,685,000
42.0	Insurance Claims & Indemnities	0	0	0
43.0	Interest & Dividends	0	0	0
44.0	Refunds	0	0	0
	Subtotal, Non-Pay Costs	**1,237,537,000**	**1,387,666,000**	**150,129,000**
	Total Budget Authority by Object	**1,303,817,000**	**1,457,915,000**	**154,098,000**

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Salaries and Expenses

OBJECT CLASSES	FY 2001 Estimate	FY 2002 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$28,779,000	$30,500,000	$1,721,000
Other Than Full-Time Permanent (11.3)	12,500,000	13,250,000	750,000
Other Personnel Compensation (11.5)	1,820,000	1,925,000	105,000
Special Personnel Services Payments (11	11,477,000	12,170,000	693,000
Total Personnel Compensation (11.9)	**54,576,000**	**57,845,000**	**3,269,000**
Civilian Personnel Benefits (12.0)	11,700,000	12,400,000	700,000
Benefits to Former Personnel (13.0)	4,000	4,000	0
Subtotal, Pay Costs	**66,280,000**	**70,249,000**	**3,969,000**
Travel (21.0)	2,109,000	2,300,000	191,000
Transportation of Things (22.0)	360,000	395,000	35,000
Rental Payments to Others (23.2)	902,000	1,000,000	98,000
Communications, Utilities and Miscellaneous Charges (23.3)	1,640,000	1,800,000	160,000
Printing and Reproduction (24.0)	900,000	980,000	80,000
Other Contractual Services:			
Advisory and Assistance Services (25.1)	1,682,000	1,867,000	185,000
Other Services (25.2)	3,692,000	4,098,000	406,000
Purchases from Govt. Accounts (25.3)	70,685,000	78,260,000	7,575,000
Operation & Maintenance of Facilities (25.	5,184,000	5,704,000	520,000
Operation & Maintenance of Equipment (2	1,696,000	1,883,000	187,000
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**82,939,000**	**91,812,000**	**8,873,000**
Supplies and Materials (26.0)	14,318,000	15,893,000	1,575,000
Subtotal, Non-Pay Costs	103,168,000	114,180,000	11,012,000
Total, Administrative Costs	**169,448,000**	**184,429,000**	**14,981,000**

National Institute of Diabetes and Digestive and Kidney Diseases

SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE

HOUSE

FY 2001 House Appropriations Committee Report Language (H.Rpt. 106-645)

Item

Bone Diseases **--** The Committee urges NIDDK to enhance research on osteoporosis and other disorders of calcium metabolism, including renal osteodystrophy, which occurs in patients with chronic kidney disease. NIDDK is also encouraged to enhance its efforts in the areas of nutritional and hormonal influences on calcium and skeletal status and functional genomics in bone. The Committee encourages the Institute to work with NCI to focus on cancer that spreads to bone. (p.67)

Action Taken or to be Taken

The NIDDK has a strong program on bone and mineral research. This program encompasses both basic and clinical research on hormonal regulation of bone and mineral metabolism in health and disease. Areas of support include endocrine aspects of disorders affecting bone, including osteoporosis, Paget's disease, renal osteodystrophy, hypercalcemia of malignancy; the progression, diagnosis and therapy of parathyroid disorders, including primary and secondary hyperthyroidism; studies of calcium balance, absorption, metabolism, and excretion; basic and clinical studies of vitamin D; the effect of cytokines (proteins released by a cell that act as mediators of an immune response), growth factors, hormones and their receptors on bone metabolism; and the role of developmental factors in bone formation.

Bone represents a target for metastasis of tumors originating in the breast and prostate, with tumor-derived growth factors or cytokines disrupting the local bone hormonal environment to give rise to inappropriate bone turnover. In the adult, a key hormone regulating bone mineral balance is parathyroid hormone (PTH), which, together with its receptor, was identified and characterized over many years by NIDDK-supported investigators, including NIDDK intramural scientists. Subsequent identification and characterization of the parathyroid hormone related peptide (PTHrP) helped to pinpoint the cause of hypercalcemia of malignancy resulting from tumor-derived production of PTHrP which leads to calcium leaching from bones. The NIDDK currently supports research on the role of hormones that regulate bone metabolism in breast and prostate cancer.

In April 1999, a research solicitation, co-sponsored by the National Cancer Institute (NCI), NIDDK, National Institute on Aging (NIA), and National Institute of Environmental Health Sciences (NIEHS), was issued to further research in the biology, development and progression of malignant prostate disease. This announcement was developed in response to recommendations of

the Prostate Cancer Progress Review Group, established to help the NIH define and prioritize the national research agenda for prostate cancer. The ultimate goal of this solicitation is to further understanding of key concepts of prostate cancer biology, and identify means to exploit such information to prevent, diagnose and treat prostate cancer.

In December 1999, the NIDDK, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Dental and Craniofacial Research (NIDCR), NIA, and National Institute of Child Health and Human Development (NICHD) issued a research solicitation on receptors and signaling in bone health and disease. Diseases that affect bone, such as osteoporosis and primary hyperparathyroidism, result in gradual loss of bone and resulting thinning of the bone (osteopenia), a leading cause of fracture in adults. Hormones are major regulators on bone mass, and osteopenia may result from alterations in hormone action, such as loss of normal estrogen production in post-menopausal women, excessive production of PTH as in primary hyperparathyroidism, or glucocorticoid excess as a consequence of chronic steroid use in immunosuppressive therapy. Limited clinical trials have determined that hormone replacement can partially mitigate or reverse the osteopenia associated with menopause or primary hyperparathyroidism. The use of estrogen/progesterone hormone replacement therapy has gained wide acceptance in peri- and post-menopausal women, though not without undesired side effects. The development and use of Selective Estrogens Receptor Modulators (SERMS) has served to partially offset the side effects while giving some degree of protection against post-menopausal bone loss. Still other therapeutic agents have been developed that alter mineral content and/or molecular structure of bone or that alter hormonal balances. It is hoped that this solicitation may further basic research in the area of hormonal regulation of bone cell structure and function and possibly lead to the development of therapeutic agents for the treatment of diseases which adversely affect bone, including osteoporosis and primary hyperparathyroidism.

As a result of NIDDK research initiatives, considerable progress has been made in understanding the roles of hormones, growth factors, and cytokines in the regulation of bone. New developments in understanding hormonal mechanisms underlying the regulation of bone formation on one hand, and bone loss on the other, make it possible to develop new therapeutic agents to properly regulate bone turnover and potentially rebuild bone.

The NIH sponsored a Consensus Development Conference in *Osteoporosis Prevention, Diagnosis and Therapy* on March 27-29, 2000, in which the NIDDK participated. The panel's recommendations for future research include identifying and intervening in disorders that can interfere with peak bone mass in children of ethnic diversity; improving diagnosis and treatment of secondary causes of osteoporosis; collecting the data necessary to establish testing guidelines; developing quality-of-life measurement tools; conducting randomized trials of combination therapies; and developing a paradigm for the management of fractures.

The NIDDK supports a number of research projects on the regulation of bone formation in renal failure. Results from these studies are providing new insights into renal bone disease and will aid in the development of effective strategies for prevention. The NIDDK also disseminates

information for dialysis patients about how high levels of phosphorous in the blood lead to loss of calcium from bones, making them weak and likely to break, and how the body uses vitamin D to help absorb calcium.

Item

Cooley's Anemia -- The Committee has long supported research in the area of Cooley's anemia. Due to the numerous red blood cell transfusions that patients receive, iron accumulates in the major organs, particularly the heart and liver. The effective removal of this iron by chelating drugs requires an accurate assessment of iron levels in the patient. Accuracy is impeded by the lack of a high quality, non-invasive test to measure iron levels. The Committee understands that a new technology has been developed which holds promise in addressing this problem and urges NIDDK to test its efficacy with Cooley's anemia patients through all available mechanisms, as appropriate. The Committee remains interested in the research progress being made with regard to the development of safe and effective iron chelator drugs that are less troublesome than those currently used, as well as the development of drugs for the regulation of hemoglobin synthesis. (p. 67)

Action Taken or to be Taken

In FY 2001, the NIDDK will convene a workshop to discuss issues and to help in the design of the most effective approach to non-invasive iron measurement in patients. The need for this type of measurement has been long-recognized in thalassemia patients who receive chronic blood transfusions. More recently, sickle cell anemia patients at risk for stroke have been transfused more regularly, and there has been consideration of iron measurements in individuals with hemochromatosis mutations. There are numerous other conditions where such measurement might be useful.

The potential of several technologies will be discussed at the workshop. For many years, thalassemia patients have had their liver iron stores assessed using a SQUID (superconducting quantum interference device), which has been shown to correlate well with biopsy results.

Another technology that has been proposed for such measurements is magnetic resonance imaging (MRI). Several other methods have also been considered, including nuclear resonance scattering of X-rays and computed tomography.

With regard to hemoglobin synthesis, the NIDDK also will encourage new avenues of research into the developmental processes involved in the differential expression of globin genes. The emphasis is on understanding the mechanisms of regulation of fetal hemoglobin synthesis, and development of new approaches of stimulation of fetal hemoglobin in patients with Cooley's anemia and other similar blood disorders.

One long-standing interest of the NIDDK is research aimed at the development of iron chelating drugs for treatment of the iron overload of thalassemia, for which, currently, desferrioxamine is the only FDA approved therapy. Chronic treatment with this drug is cumbersome and painful and often provides inadequate lifetime control of iron stores. Advances related to an increased understanding

of molecular and biochemical pathways of iron metabolism, understanding of fundamental mechanisms of iron chelator action, and improved rational drug design techniques may offer an opportunity to undertake a more systematic approach to the problem faced by Cooley's anemia patients. The NIDDK is continuing its substantial investment in this area, with a new drug, HBED, developed under an NIDDK contract being evaluated for human trials. Application has been filed with the FDA for investigational new drug status for this compound and animal studies to date are extremely promising.

Item

Diabetes **--** Diabetes remains a leading cause of early death and disability and affects approximately 16 million Americans. The Committee urges NIDDK to significantly enhance its support of diabetes research following the recommendations made in the Diabetes Research Working Group report. NIDDK is further urged to focus increased resources for research related to juvenile, or Type 1, diabetes. A 1999 Institute of Medicine report concluded that development of a vaccine to treat or prevent Type 1 diabetes would bring exceptionally high health and economic benefits to society and the Diabetes Research Working Group recommended that a major effort be launched in this area. The Committee encourages NIDDK, in collaboration with NIAID and NICHD, to enhance research to develop a vaccine to prevent juvenile, or Type 1, diabetes. The Committee requests that the Director of the Institute be prepared to provide a status of this initiative at the fiscal year 2002 appropriations hearing. The Committee also urges NIDDK, working with NHGRI and NICHD, to enhance its effort to identify the genes associated with Type 1 diabetes and requests that the Director of the Institute also be prepared to provide a status of this initiative at the fiscal year 2002 appropriations hearing. (p. 67)

Action Taken or to be Taken

In March 2000, the Department of Health and Human Services (DHHS) submitted a report to the Senate Labor/HHS Appropriation Subcommittee describing many examples of new and significantly expanded research initiatives undertaken thus far to exploit the scientific opportunities and meet the research needs identified by the Diabetes Research Working Group (DRWG), especially as they relate to type 1 diabetes. In June 2000, the DHHS also submitted a report to the Congress on trans-NIH research initiatives undertaken with special funds for type 1 diabetes research provided by the Balanced Budget Act of 1997. Some examples of program development are described below.

In pursuing the extraordinary opportunity of islet transplantation research identified by the DRWG, the NIDDK, in a collaborative effort with the NIAID and the Juvenile Diabetes Research Foundation International (JDRF), has funded six centers to develop improved protocols for islet cell transplantation into humans. In addition, the NIDDK Division of Intramural Research, in collaboration with the Department of Defense, the NIH Clinical Center, and the Diabetes Research Institute of the University of Miami, has initiated a clinical research program that will explore new approaches to both kidney and islet cell transplantation for diabetes. The NIDDK and the Juvenile Diabetes Research Foundation International are cosponsoring the Immune Tolerance Network (ITN) research initiative, spearheaded by the NIAID. The ITN will solicit, develop, implement, and

address clinical strategies and biological assays for the purpose of inducing and maintaining immune tolerance in patients receiving kidney and islet transplants. The NIDDK Organ/Tissue Transplant Research Center will be one of ten centers participating in the ITN, which will adopt the "Edmonton Protocol" for performing approximately 40 islet transplant procedures. This new technique, developed by researchers at the University of Alberta, Canada, garnered international headlines after the announcement that a number of patients with type 1 diabetes treated with islet transplants remained insulin free for up to 14 months following the procedure. The trial will attempt to further assess the effectiveness of the technique and identify any long-term risks associated with steroid-free immunosuppressive therapies. Researchers hope the trial will serve as a platform for testing new treatments in which the permanent reversal of diabetes can be achieved without the need for immune suppressing therapies. In addition, the NIDDK will support two additional studies to determine if one pancreas can provide sufficient islets for transplantation. The "Edmonton Protocol" requires two pancreata to yield sufficient islet cells for one transplant.

Also in response to major DRWG recommendations, the NIDDK has several new or expanded research initiatives planned for FY 2001 related to the pancreas and the beta cell. In FY 1999, the NIH initiated a project entitled, "Functional Genomics of the Developing Pancreas," which will identify novel genes useful for developing strategies in beta cell replacement and modulation of autoimmune beta cell destruction. The ongoing program will develop comprehensive microarrays of genes expressed in the beta cell, allowing investigations of global gene expression in islets from mouse models of diabetes and in islets from humans. An expression profiling database is under development that will allow all investigators access to these data, and will promote progress in the differentiation and regeneration of beta cells. In FY 2001, the NIDDK proposes to establish a Beta Cell Biology Consortium to build upon the ongoing Functional Genomics of the Developing Pancreas Consortium. The Beta Cell Biology Consortium will target the following research areas: beta cell development, prospective identification and purification of pancreatic stem/progenitor cells from the mouse and adult human, development of clonogenic assays for evaluating potential stem cells from the mouse and adult human, evaluation of pancreatic islets for transplantation, functional imaging of the beta cell, and cell culture models of the human pancreatic beta cell. The NIDDK will support a research initiative to develop a transgenic mouse model to fuel the development of definitive assays to determine whether pancreatic stem cells exist in the mouse and adult human in response to recommendations from an NIDDK-sponsored conference.

In the area of the genetics of type 1 diabetes, the NIDDK and the JDRF held a meeting in November 2000, to explore the establishment of a Type 1 Diabetes Genetic Consortium. Three genome-wide scans for type 1 diabetes have recently been completed and have identified several loci as containing a diabetes susceptibility gene. A combined analysis of these three datasets could identify the most promising loci for further studies. The NIDDK may provide support for the creation of a common database and other analyses needed to foster this Consortium effort.

The NIDDK also supports a number of ongoing investigator-initiated studies on the epidemiology and etiology of type 1 diabetes. Resultant data will provide clues as to the pathogenesis of type 1 diabetes, the time course and characteristics of the disease and risk factors for progression. Data will also assist in the design of intervention strategies and the identification of populations to be tested in future studies.

The NIDDK, in conjunction with the National Heart Lung and Blood Institute (NHLBI) and the National Institute of Allergy and Infectious Disease (NIAID), has issued a research solicitation in the area of gene therapy for type 1 diabetes and its complications based on recommendations from a workshop held in November 1999. The workshop, entitled "Gene Therapy Approaches for Diabetes and Its Complications," was co-sponsored by NIAID, National Center for Research Resources (NCRR), NHLBI, the American Diabetes Association, and the Juvenile Diabetes Research Foundation International.

Regarding vaccine development, the NIH is actively pursuing research in the area of a vaccine for type 1 diabetes. In 1999, an Institute of Medicine report, "Vaccines for the 21st Century: A Tool for Decision Making," highlighted the need for vaccines for type 1 diabetes and other autoimmune diseases. Much of the basic research on type 1 diabetes that the NIDDK supports will facilitate the establishment of a solid knowledge base enabling the selection, development, and testing of promising candidate agents for type 1 diabetes, including potential therapeutic vaccines and preventive vaccines. In addition, the NIDDK, in collaboration with other NIH Institutes, supports a type 1 diabetes primary prevention trial-- the Diabetes Prevention Trial for Type 1 Diabetes (DPT-1). The current number of clinical centers and associated networks of recruitment/retention sites for DPT-1 will be expanded to approximately 20 in order to complete the DPT-1 and to form the basis of an enhanced network that will comprise the "Type 1 Diabetes TrialNet." The TrialNet centers will provide the patient population and infrastructure to test additional promising new strategies to prevent or delay progression of type 1 diabetes. Also, the NIDDK recently released a research solicitation on new strategies for the treatment of type 1 diabetes, including immunomodulation therapies to reverse or arrest the disease. The NIAID and the NIDDK, with funds from the Balanced Budget Act of 1997, will be launching a program with the long-range objective of developing vaccines to prevent autoimmune diseases. This research initiative will assure support, within this larger framework, for the immunological groundwork needed for the development of diabetes preventive approaches. In addition, representatives of the NIAID, NIDDK and the Juvenile Diabetes Research Foundation International met recently with public health officials in Australia to coordinate their ongoing efforts to develop a vaccine for type 1 diabetes with those efforts recently initiated in the U.S.

Item

Type 2 Diabetes -- Programs that raise awareness of diabetes and its risk factors are important to improving the lives of all people affected by diabetes. For example, many people diagnosed with type 2 diabetes don't show overt signs of the disease prior to diagnosis. Also, African Americans, Hispanics, and Native Americans are at an increased risk for the disease. The Committee urges the Institute to continue to expand promising basic research and clinical trials to improve early detection and treatment of diabetes, and to find a cure for the disease. (p. 67-68)

Action Taken or to be Taken

The NIDDK supports a number of research initiatives aimed at raising public awareness of diabetes, including the National Diabetes Education Program (NDEP), which the NIDDK supports in

partnership with the Centers for Disease Control and Prevention, the National Center for Minority Health and Health Disparity and 150 participating organizations. In June 1998, the NDEP launched a media campaign to disseminate the message that diabetes is serious, common, costly, yet controllable. Because of the extremely high incidence of diabetes in all minority groups, the NDEP quickly moved to target these audiences, developing culturally-sensitive public health messages tailored to specific minority groups. Complementing these education campaigns are the efforts of the National Diabetes Information Clearinghouse (NDIC), established to increase knowledge and understanding about diabetes among patients, health care professionals, and the public. The NIDDK has also established a new Office of Minority Health Research Coordination which has developed a strategic plan to strengthen research on diseases within the NIDDK mission that place a disproportionate burden on minority groups, such as type 2 diabetes.

A major risk factor for the development of type 2 diabetes is obesity. The institute is coordinating the Action for Health in Diabetes (Look AHEAD) Trial. The Look AHEAD Trial will begin recruitment in Spring 2001 of approximately 6,000 obese patients with type 2 diabetes at 16 locations throughout the U.S. A goal of the trial is to have the overall ethnic and racial composition of the recruited patient population reflect the prevalence rates for diabetes in the U.S.

The Diabetes Prevention Program (DPP) is a large multicenter clinical trial of primary prevention strategies for patients at high-risk for developing type 2 diabetes. This trial is being conducted at 27 centers across the U.S. The DPP has now completed patient recruitment, with a total of over 3,800 participants--45 percent of whom are from minority groups. We expect that findings from this clinical trial will advance our understanding of the factors that lead to the development of type 2 diabetes and aid in pinpointing effective prevention strategies for high-risk populations.

The NIDDK is pleased to report on a number of new basic and clinical research initiatives both under way and planned with respect to research on or relevant to type 2 diabetes. The NIDDK is soliciting research on the following topics: type 2 diabetes in the pediatric populations; new therapies for diabetic foot disease; mouse metabolic phenotyping centers for models of diabetes complications; endothelial cell damage in complications of diabetes; development of the endocrine pancreas; growth factors in diabetes complications; and insulin signaling and receptor cross-talk; treatment of type 2 diabetes in minority children; and the diabetes genome anatomy program.

In FY 2001, the NIDDK plans to support research in the area of racial and ethnic disparities in the incidence of diabetes complications. The goal of this research initiative is to determine whether minority racial/ethnic populations continue to differ in their risk for microvascular and macrovascular complications of diabetes, and, if so, the reasons for these differences. A second research solicitation for FY 2001 will support studies in representative U.S. populations to determine the reasons for disparities in the incidence of type 2 diabetes in minority racial/ethnic populations.

In July 1999, the Diabetes Mellitus Interagency Coordinating Committee (DMICC) convened a group of epidemiologists and pediatric endocrinologists to address the alarming increase of type 2 diabetes in children, especially children from minority populations. Based on data presented at that meeting, the NIDDK and the NICHD have issued a solicitation to stimulate research on the causes,

mechanism, prevention, and treatment of type 2 diabetes in children.

The DMICC met in May 2000 with a committee of American Indian tribal leaders to exchange ideas on the problem of type 2 diabetes in American Indian children. The goal of this meeting was to foster cooperation between tribal Nations and diabetes investigators in the development of effective, culturally sensitive approaches to prevention and management of diabetes. As a result of this meeting, the NIDDK and NICHD have planned a research initiative for FY 2001 that will encourage increased research in the prevention and treatment of type 2 diabetes in minority children, with a special emphasis on children from Native American communities.

Research initiatives the NIDDK plans to expand or extend in the future include the Type 2 Diabetes Genetics Consortium; the National Diabetes Education Program; and the Family Investigation of Nephropathy and Diabetes. The NIDDK has also agreed to co-sponsor the *Bypass Angioplasty Revascularization Initiative II* (BARI II) Clinical Trial and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Clinical Trial with the NHLBI. These research initiatives will further the goal of the NIDDK and the NIH to improve the early detection and treatment of diabetes and to find a cure for this devastating and costly disease.

Item

Digestive Diseases -- .... The Committee continues to encourage NIDDK to strike an appropriate balance between conducting basic studies on digestive diseases and bringing those research findings to the bedside in the form of improved patient care. (p. 68).

Action Taken or to be Taken

Concerted efforts continue to bring forward into the clinical setting promising results of basic studies from the laboratory. Through the use of an ongoing Program Announcement for planning grants (RO3s), the Institute promotes pilot studies that will help pave the way to full-scale clinical trials in digestive diseases. These trials are designed to provide a scientific basis for improvements in the standard of care. The portfolio of clinical trials in digestive diseases has grown over the last five years from less than $1 million yearly to more than $6 million yearly. It now includes studies in such diverse areas as functional bowel disorders, prevention of ulcer hemorrhage, esophageal varices, upper gastrointestinal hemorrhage, and reduction of hepatitis C virus recurrence after liver transplantation. The NIDDK, working with the CDC and other organizations, also plans to establish a coordinated information program about hepatitis C in African Americans and Hispanic/Latino Americans. The goal of this research initiative is to identify additional needs of patients, families and physicians and to develop messages and materials to address these needs.

Item

Endoscopic Research -- The Committee is pleased that NIDDK is funding the Clinical Outcomes Research Initiative. This national network of specialists in gastrointestinal diseases utilizes a national endoscopic database to study important issues related to gastrointestinal endoscopy which

will form the basis for a variety of new clinical studies in gastroenterology. NIDDK is encouraged to continue to support endoscopic research. (p. 68)

Action Taken or to be Taken

As a result of a Request for Applications published last year, NIDDK has awarded a grant that will support research activities generated by an established endoscopic data center. Working with a number of clinical affiliates, the data center will provide endoscopic reports in multi-center studies in areas such as Barrett's esophagus, colon surveillance for neoplasia, and chronic pancreatic disease.

Item

Hepatitis C -- The Committee is pleased that NIDDK has made an award for a large scale hepatitis C clinical trial that will involve over 1,000 patients and nine states around the country. This trial, known as the HALT-C trial, is expected to yield important scientific discoveries regarding the relatively low response rate to current hepatitis C treatments. The large number of individuals involved in this trial offers significant opportunities for ancillary studies including the influence of genetic factors, the rate and cause of viral mutations, and improved scientific knowledge to better understand the wide range of reactions of hepatitis C patients to treatment protocols. The Committee urges NIDDK to enhance efforts to research these ancillary research opportunities. (p. 68)

Action Taken or to be Taken

The HALT-C trial will focus on means of prevention of cirrhosis and liver cancer in hepatitis C patients. Ancillary studies connected with the trial have been reviewed for potential co-funding by the National Institute of Allergy and Infectious Diseases (NIAID) and industry. Using data collected before, during and after therapy, the studies will focus on such areas as the non-invasive assessment of liver fibrosis; how the hepatitis C virus replicates; risk factors for progression, including nutrition, obesity, smoking, and alcohol; and the role of genetic diversity in diagnosis and clinical management of hepatitis C.

Item

Hypertension and Kidney Disease -- The Committee urges NIDDK to collaborate with NHLBI on research related to hypertension and its relationship to kidney disease through all available mechanisms, as appropriate, including sponsoring a workshop to define areas of research for potential joint projects. The Committee requests that the Director of the Institute be prepared to testify on the progress in this area at the fiscal year 2002 appropriations hearing. (p. 68)

Action Taken or to be Taken

In the past and up to the present, the NIDDK and the National Heart, Lung, and Blood Institute (NHLBI) have collaborated extensively on research activities related to hypertension and kidney

disease. For example, both institutes have been conducting large-scale multicenter clinical trials–the African American Study of Kidney Disease and Hypertension (AASK) and the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack (ALLHAT) Trial–on the treatment of hypertension, addressing related but different research questions regarding the effects on kidney disease. There has been periodic consultation between the staffs of the respective institutes regarding these trials, as well as on broader research issues related to the prevention of chronic kidney failure. Indeed, the two Institutes will be working closely as the AASK and ALLHAT trials are completed, planned for 2001 and 2002 respectively. Both trials will produce important information on how the treatment of hypertension affects the progression of renal disease. The implications of these data for practice guidelines, for future intervention studies, and for our understanding of hypertensive renal disease will need careful assessment.

Another major area of cooperation is in understanding the fact that patients with chronic renal insufficiency have accelerated rates of cardiovascular disease. The NIDDK is providing supplementary funding to several large NHLBI projects (Action to Contradict Cardiovascular Risks in Diabetes [ACCORD] and Bypass Angioplasty Revascularization Investigations [BARI] II Diabetes Trial) that will address this issue. As the main protocols for these trials are finalized, there will be consideration of ancillary studies that have the potential for enlarging understanding of the interplay of diabetes and blood pressure levels and their treatments as they affect renal damage and function.

The NIDDK and NHLBI regularly participate in sponsorship of conferences that address common areas of concern, a notable example of which is a recent NIDDK sponsored workshop on Cardiovascular Disease in Renal Disease Patients which included several speakers from NHLBI who addressed epidemiologic strategies for studying the progression of renal disease. The NHLBI and the NIDDK are also working closely in areas of common concern, for example the cardiovascular complications of diabetes, where the institutes have similar goals to develop and distribute better animal models to address this important public health problem.

A considerable level of NHLBI-NIDDK cooperation and collaboration in relevant areas has existed for over a decade, and this will continue without further stimulation. The ideal time for a major conference to identify new directions–both at the basic/clinical and population-based levels–perhaps lies two to three years in the future, when the results of major ongoing studies are available.

Item

Inflammatory Bowel Disease -- ....The Committee continues to encourage NIDDK to give priority consideration to investigation into the cellular, molecular, and genetic structure of IBD, identification of the genes that determine susceptibility or resistance to IBD in various patient subgroups, and coordination and integration of basic investigations designed to clarify mechanisms of action and disease pathogenesis into clinical trials, as described in the recent research agenda developed by the scientific community entitled “Challenges in Inflammatory Bowel Disease.” The Committee recognizes the success of the digestive disease centers program in addressing a wide range of disorders and encourages NIDDK to expand this program with an increased emphasis on IBD. (pp. 68-69)

Action Taken or to be Taken

Inflammatory bowel disease (IBD) continues to be an area of NIDDK research emphasis. Plans are under way to organize a research workshop to be held in FY 2001 on the genetics of IBD. This workshop is expected to result in issuance of a Request for Applications for a consortium on the genetics of IBD that would be funded in FY 2002. To increase the effectiveness of research initiatives in IBD research, the NIDDK is in the process of recruiting an expert in IBD research to lead this activity.

NIDDK currently supports 13 digestive disease research centers and has plans to expand that number to 14 centers in FY 2001. A new Digestive Diseases Research Center was funded in FY 2000 that focuses on infections of the gastrointestinal tract and their control. Two other centers that conduct research in inflammatory bowel disease successfully recompeted for funding in FY 2001. The sole focus of one of these Centers is research in IBD.

Item

Irritable Bowel Syndrome -- The Committee remains concerned about the increasing frequency of irritable bowel syndrome (IBS), a chronic complex of disorders that malign the digestive system. These common dysfunctions strike people from all walks of life and result in tremendous human suffering and disability. The Committee encourages NIDDK to provide adequate funding for IBS functional bowel disorders research through all available mechanisms, as appropriate, including education/scientific symposiums. (p. 69)

Action Taken or to be Taken

NIDDK funding for research in functional bowel disorders has nearly doubled from FY 1996 to FY 1999. The Institute supported a scientific workshop on "Motility of the Digestive Tract" in 1998 that led to a research initiative on "Integrative Approaches to the Study of Motility of the GI Tract." This Request for Applications was co-supported by the Office of Research on Women's Health and the American Digestive Health Foundation. Seventeen grants were funded as a result of this activity – four in FY 1999 and 13 in FY 2000. In follow-up to the Request for Applications, the NIDDK plans to issue a Program Announcement in FY 2001 requesting grant applications that would apply state-of-the art molecular techniques to enhance understanding of the enteric nervous system, gastrointestinal motility, and motility disorders, especially those that affect children. To date, 10 more grants have been funded in this area.

Item

Interstitial Cystitis -- The Committee urges NIDDK to enhance research on interstitial cystitis (IC) and further explore the many promising preliminary research findings on this chronic debilitating disease. The Committee is pleased that NIDDK has initiated a study of the epidemiology of IC and requests that the Director be prepared to provide a status of this initiative at the fiscal year 2002

appropriations hearing. The Committee encourages the Institute to expand minority enrollment in clinical centers through all available mechanisms, as appropriate. (p. 69)

Action Taken or to be Taken

The NIDDK recently implemented a research initiative entitled "Epidemiology of Chronic Pelvic Pain of the Bladder and Interstitial Cystitis." The FY 2001 awards that will result from this activity will include longitudinal epidemiology studies on the incidence of syndromes associated with pelvic pain and chronic urinary symptoms. There are relatively few minority women in the Institute's current interstitial cystitis study centers, even though some of these programs serve populations with substantial minority representation. It is not clear whether this represents genuine differences in the incidence of the disease or differences in health care availability and referral patterns. The studies being encouraged by the research initiative should address these issues, and allow targeted approaches to the populations most impacted by this disease.

In October 2000, the NIDDK supported an international research symposium on interstitial cystitis and bladder research. This meeting presented new findings on the cell biology, neurobiology, genetics, and immunology of the urinary bladder, as well as reports of recent findings on biomarkers in interstitial cystitis and other bladder disorders. Descriptions of potentially associated syndromes were presented, as well as novel therapeutic approaches. Future directions for research were identified.

Item

Kidney Disease Education -- . . . .The Committee urges NIDDK to enhance its education efforts to bring advances in medical care to the public. The Committee requests that the Director of the Institute be prepared to testify on this issue at the fiscal year 2002 appropriations hearing. (p. 69)

Action Taken or to be Taken

NIDDK will continue planning a National Kidney Disease Education Program by sponsoring one or more planning conferences involving researchers, voluntary and professional organizations, health care providers and public health practitioners from academia, government, industry and groups representing diverse racial and ethnic populations. NIDDK will establish an executive committee to focus the program's overall vision, goal, objectives, and direction, and to document the science base for an education program, including incidence, prevalence and the current environment for the diagnosis, prevention, and treatment of kidney disease.

In July 2000, the NIDDK convened an ad hoc Kidney Disease Education Task Force to obtain advice from a cadre of individuals with substantial expertise in health policy, education, and preventive medicine. The group identified areas of consensus that are appropriate starting points for an education or outreach program, areas that may be ripe for consensus, and areas needing further research. The group placed high priority on developing outreach programs targeting high-risk minority populations, especially African Americans, Native Americans, and Hispanic

Americans, emphasizing treatments for which scientific consensus already exists.

Item

Kidney Genome Anatomy Program --. . . . The Committee encourages NIDDK to explore the feasibility of creating a kidney genome anatomy program to determine which genes are expressed/suppressed in kidney disease. (p. 69)

Action Taken or to be Taken

The NIDDK is supporting research programs that encourage exploration into the genetic components of kidney diseases and development of new technologies for this purpose. Around the world, the study of genetic expression and molecular interactions is leading to new insights into many kidney diseases. In FY 2001, the NIDDK will establish Biotechnology Centers that will provide genomic profiling resources to investigators. The kidney research community is expected to be well represented in this effort. In addition, NIDDK scientists have located and sequenced two genes for polycystic kidney disease (PKD), and now are pursuing study of the complex of genetic mechanisms that influence the severity of PKD. The Institute also is sponsoring research on genetic factors in the development of the kidney disease caused by diabetes. Through the "Familial Investigation of Nephropathy of Diabetes (FIND)" program, new gene sequencing techniques will be used to study kidney function and kidney failure. In FY 2001, the NIDDK plans to expand the FIND study to create a sample repository and to create immortalized cell lines from each recruited patient as a renewable resource for DNA for genetic analyses, to include additional minority patients, and to expand the FIND sample by addition of the well-phenotyped patients from the Institute's African American Study of Kidney Disease and Hypertension Trial.

Also in FY 2001, the NIDDK will pursue investigations of genes that are relevant to the kidney by beginning to expand the Institute's ongoing Diabetes Genome Anatomy Program (DGAP) to include not only the pancreas, but also other major organ systems affected by diabetes and its complications. Diabetes is the most common cause of end-stage kidney disease requiring dialysis in the U.S. The development of DNA array libraries and bioinformatics tools applied to normal and pathological conditions of the kidney and the endocrine, cardiovascular, genitourinary, musculoskeletal, and peripheral nervous systems should contribute to a better understanding of human physiology and spur development of diagnostic tools and therapeutic approaches aimed at reducing the burden of diabetes and its complications, including kidney disease.

In FY 2001, the NIDDK will sponsor a workshop entitled "Renal Genomics in the Post-Genomic Era," which will present state-of-the-art genomic and gene profiling methods that can be used to simplify gene discovery in the post-genome era. The workshop will also discuss methods for studying gene regulation, transcription, and function using advances gene profiling and proteomic approaches. The NIDDK has also established a strategic planning group on "Genetics, Genomics, and Bioinformatics" to help guide its future research efforts in these important areas.

Item

Liver Transplantation -- The Committee is aware of the significant and continuing shortages of livers available for transplantation, and therefore urges NIDDK to enhance research efforts that would facilitate the success of liver transplantation and the number of livers available for transplantation. The use of living liver donors may be one of the most important surgical and scientific breakthroughs that can assist people in the need of liver transplants. The Committee urges NIDDK to enhance efforts in this area through all available mechanisms, as appropriate, including sponsoring a state-of-the art conference to address the many questions surrounding this medical procedure. In addition, the Committee is aware that almost 100 percent of individuals, who have liver transplants with hepatitis C as the primary indication, become re-infected with the hepatitis C virus. While the severity of the re-infection typically can be controlled, approximately 10 percent of the cases develop severe chronic hepatitis within 2 years. NIDDK is urged to enhance efforts to minimize the re-infection rate including the evaluation of therapeutic agents that offer the potential for controlling hepatitis C re-infection. (p. 69-70)

Action Taken or to be Taken

The NIDDK sponsored a clinical research workshop on living donor liver transplantation (LDLT) December 4-5, 2000. The workshop dealt with the current status of LDLT in the United States; technical, medical and ethical issues; and the needs for further research. A major focus will be means of increasing the availability of liver transplants to more Americans, and particularly minority populations. The Institute continues to promote research in the area of re-infection of hepatitis C virus following transplantation. A Program Announcement was issued that encouraged experienced and new investigators to submit planning grants on methods for preventing the recurrence of hepatitis C infection after liver transplantation; two applications were awarded, one on prevention of hepatitis B and one on prevention of hepatitis C. During the two years of these planning grants, NIDDK staff worked closely with the investigators to develop a rigorous and practical protocol for a full-scale prevention study. These full-scale trial applications will be submitted and reviewed in the next year. NIDDK also continues to fund a long-term study on the outcome of hepatitis C after liver transplantation as a cooperative agreement and extension of the Liver Transplantation Database. This long-term study will help define the factors that predict recurrence of hepatitis C and help design interventions that might either prevent or ameliorate recurrent hepatitis C.

Item

Pediatric Digestion and Motility Disorders -- The incidence of digestion and motility disorders in children often go unrecognized and misdiagnosed and lead, in some cases, to extreme debilitation and death. The Committee encourages NIDDK to enhance research efforts to prevent, treat, and ultimately cure for these disorders in children. (p.70)

Action Taken or to be Taken

In January 1999, following a workshop on "Motility of the Digestive Tract," the NIDDK issued a Request for Applications for research on "Integrative Approaches to the Study of Motility of the Gastrointestinal Tract." The research solicitation encouraged basic and clinical research to identify effective diagnostic modalities and treatment interventions for motor disorders in adults and in infants and children. The research initiative was co-sponsored by the American Digestive Health Foundation and the NIH Office of Research on Women's Health. Seventeen grants will be funded as a result of this Request for Applications. In follow up to this effort, the NIDDK plans to stimulate more research in motility disorders with the issuance of a Program Announcement requesting applications that will apply state-of-the-art molecular techniques to enhance knowledge of the enteric nervous system, gastrointestinal motility, and motility disorders, especially those that affect children. To date, ten more grants have been funded in this area.

Item

Pediatric Kidney Disease -- . . . . the Committee encourages NIDDK to enhance its research efforts on the prevention and treatment of chronic renal failure and end-stage renal disease in children from all causes, including diabetes, hypertension, genetic kidney disease and disorders of renal development through all available mechanisms, as appropriate, including convening a scientific meeting to review the pediatric liver [kidney] disease research agenda. NIDDK also is urged to focus on new approaches to enhance or accelerate recovery from acute renal failure, which commonly occurs in hospitalized pediatric patients and accounts for substantial sickness and death. The Committee urges NIDDK to enhance research to find ways to prevent, treat, and cure pediatric liver [kidney] diseases through all available mechanisms, as appropriate, including convening a scientific meeting to review the pediatric liver [kidney] disease research agenda (p. 70)

Action Taken or to be Taken

The NIDDK interprets the language cited as pertaining to pediatric kidney disease, as stated in the heading. The NIDDK has sought to encourage research on normal kidney development and on pediatric kidney disease through several recent activities: (1) The FY 1999 research initiative on "Diabetic and Non-Diabetic Nephropathy Susceptibility Genes" funded eight research grants to identify new strategies to prevent or delay the development of progressive renal disease leading to chronic renal failure; (2) The FY 1999 research initiative on "Polycystic Kidney Disease: Innovative Imaging to Assess Progression" is supporting research to identify and test the accuracy and reproducibility of medical imaging techniques, as well as the identification of surrogate markers of disease progression, which should lead to the planning and testing of clinically appropriate interventions for polycystic kidney disease; (3) The FY 1999 research initiative on "Interdisciplinary Centers for Polycystic Kidney Disease Research" is supporting expansion, through four centers, of the basic research infrastructure in PKD. It is envisioned that this will in turn enable clinical studies to evolve more rapidly; (4) The NIDDK sponsored a meeting in November 2000 of the Task Force for an Interventional Trial in Pediatric Focal Segmental Glomerulosclerosis (FSGS). FSGS is an irreversible glomerular process which produces steroid-resistant nephrotic syndrome and has a great risk of progression to end-stage renal disease. There have been several recent insights into the genes responsible for the familial forms of this disease. The Task Force will discuss the criteria for inclusion and the nature of potential interventions for a clinical trial on FSGS of unknown origin in children, including drugs such as cyclosporin.

children, including drugs such as cyclosporin.

The NIDDK will continue to expand research on pediatric kidney diseases based on recent and emerging scientific opportunities. As part of the NIDDK's long-range planning process, several broad goals have been identified as of particular importance for research on pediatric kidney diseases. These goals are outlined in a 1999 strategic planning report of the NIDDK Task Force on Pediatric Nephrology Research. The Institute will consider the recommendations contained in the Task Force's report in developing future program research initiatives in pediatric nephrology.

Item

Polycystic Kidney Disease --. . . . The Committee urges NIDDK to pursue all of the new avenues of fundamental understanding that have come to light and to implement to the fullest extent possible the PKD Strategic Planning Workshop Report developed by NIDDK in fiscal year 1999. (p. 70)

Action Taken or to be Taken

In November 1998, the NIDDK and Polycystic Kidney Research Foundation sponsored a Strategic Planning Conference for PKD research. A resulting report recommended three opportunities for expansion of NIH PKD research. The NIDDK moved to develop and implement three research initiatives, two of which address recommendations in the report. First, in FY 1999, the Institute issued a request for applications to encourage development of state-of-the-art imaging methods for PKD. The primary goal of this research initiative is to test whether imaging techniques can provide sufficiently accurate and reproducible markers of progression of renal disease in PKD to permit their use in clinical trials. The NIDDK funded the Data Coordinating and Imaging Analysis Center and, in FY 2000, funded three Participating Clinical Centers. In FY 2001, the NIDDK plans to add ultrasound imaging methods and increased investment in image processing algorithms to this ongoing study. The second research initiative established four Specialized Centers for Polycystic Kidney Disease Research in FY 1999. These Centers are expanding the basic research infrastructure in PKD. The studies should foster and extend the development of new approaches into the causes, early diagnosis, and improved treatments for PKD. The products of this research should facilitate the pace at which clinical studies can evolve.

New in FY 2001 is a planned research initiative for a multi-center interventional clinical trial to assess the best strategy for reducing morbidity and mortality in PKD. A cohort of 2,000 patients is expected, with a planning phase beginning in FY 2001. The main issues to be addressed are the optimum target levels for blood pressure control, and whether angiotensin-converting enzyme inhibitors offer superior benefit over other antihypertensive agents in slowing the progression of PKD.

Item

Prostatitis --. . . .The Committee urges the Institute to expand involvement in studies of various minority groups through all mechanisms available, as appropriate, including the solicitation of

applications from investigators with diverse backgrounds. The Committee also encourages NIDDK to expand outreach efforts to include educational materials directed at primary care physicians, the urology community, and patients and the general public. (p. 70/71)

Action Taken or to be Taken

The NIDDK is supporting several new research activities related to prostatitis. One, the Chronic Prostatitis Collaborative Research Network, is developing and following a cohort of patients who meet the NIDDK definition of chronic prostatitis, which can be used to clarify the clinical and epidemiological characteristics of this disorder. In FY 2001, the Network will be expanded by addition of new clinical facilities to strengthen the recruitment of African American men with chronic prostatitis. Additional support will be provided to other centers with access to minority populations to provide support for personnel trained in minority recruitment. Patient recruitment at these clinical centers will significantly increase the enrollment of minority patients in the Network cohort and enable statistically significant data analyses. The NIDDK also plans to support expansion of the Network to permit randomized, double-blinded, placebo-controlled trials of innovative approaches to the treatment of chronic prostatitis.

The NIDDK and the American Prostatitis Foundation hosted the third annual meeting of the International Prostatitis Collaborative Network in October 2000. This meeting reviewed current advances in the basic and clinical science of chronic prostatitis and continued development of an international cohort of patients who fit the NIDDK criteria for the disease. This meeting fostered international discussion and collaboration in research on chronic prostatitis.

Item

Urological Diseases --. . . . The Committee continues to encourage NIDDK to enhance its research on the prevention, diagnosis, and treatment of urological diseases. The Committee also urges NIDDK to evaluate its urology research program to determine if it is meeting the public health needs in this area. (p. 71)

Action Taken or to be Taken

The NIDDK is establishing a Progress Review Group (PRG) for bladder diseases, which will serve as a task force for a major strategic review of current NIDDK programs in bladder research, and also to develop the future research agenda for bladder research at the NIDDK and NIH. Prominent members of the scientific, medical, and advocacy communities will comprise the PRG. The Institute convened a preliminary meeting of the PRG in February 2001, and plans to hold a larger meeting later in 2001.

The NIDDK recently has implemented, expanded, or planned several research initiatives that

address urological diseases. For example, the NIDDK has initiated an epidemiologic study of bladder diseases and disorders, called "Urologic Diseases in America." An award for this database project is anticipated for FY 2001. In addition, the Institute recently implemented an activity to encourage research on the epidemiology of chronic pain of the bladder and interstitial cystitis. Awards for cooperative agreements, up to a total of $1.5 million, will be made in FY 2001. Also, in FY 2001, the Institute plans to expand its Urinary Incontinence Treatment Network to allow additional important clinical studies. The Network will assess the long-term outcomes of the most commonly used interventions to correct urinary incontinence in adult women and the utilization of concomitant medical and behavioral therapy.

In FY 2001, the NIDDK will launch an information program, called the "Urinary Incontinence Awareness Campaign," to reach African American and Hispanic and Latino American women, especially those with diabetes. The Institute is planning to develop additional culturally-sensitive messages and materials, working with public and private partners representing African Americans and Hispanic and Latino Americans to identify additional information needs of patients, families, and physicians.

Item

Urological Diseases --. . . . The Committee urges NIDDK to increase its research into prostate growth factors and related issues toward the goal of improved diagnostic and treatment tools for BPH as well as prostate cancer and prostatitis. (p. 71)

Action Taken or to be Taken

In FY 2000, the NIDDK undertook several research initiatives to encourage investigations of prostate growth:

- The NIDDK, National Institute on Aging, National Cancer Institute, and National Institute of Environmental Health Sciences implemented a joint research initiative to explore the underlying mechanism(s) of action of hormones and growth factors in the regulation of prostate development, growth, and tumor development. Areas of focus that are envisioned will include fundamental studies of hormone and growth factor action, including the mechanisms of action of nuclear hormones, the role(s) of nuclear accessory proteins and the signal transduction pathways important for nuclear hormone action in prostate; growth factor action in prostate, including growth factors, binding proteins, receptors and signal transduction pathways; examination of the patterns of gene expression in the prostate in vivo or in prostate cells in response to hormone or growth factor action; and the development and potential use of hormone/growth factor analogs, agonists, or antagonists with potential clinical utility to modify prostate growth and tumor development and/or progression. Grants for this research will be awarded in FY 2001.

- The National Cancer Institute, NIDDK, and National Institute of Environmental Health Sciences issued a Program Announcement to fund research on molecular epidemiologic studies for advancement in understanding prostate cancer development and progression. The purpose of this research initiative is to stimulate development and application of biological markers of prostate cancer risk and tumor aggressiveness and for utilization in

chemoprevention studies. Of special interest are studies of markers to elucidate multiethnic differences in prostate cancer susceptibility. Grants for this research may be awarded in FY 2001.

- The NIDDK and the National Institute of Environmental Health Sciences implemented a joint research initiative to encourage research on cell-specific delineation of prostate and genitourinary development, including studies on the development of new research tools and methods to study development and biology of the prostate and genitourinary tract; systematic assessment of gene expression in specific cell types in the developing prostate and genitourinary tract; methods to tag individual cell types for purification, analysis, and characterization; tools to manipulate gene expression in vivo in individual cell types; and development of clinically relevant cell lines. Grants for this research were awarded in late FY 2000.

In FY 2001:

- The NIDDK is planning a research initiative on alternative and complementary therapies for symptomatic benign prostatic hyperplasia (BPH). Alternative medicine approaches to the treatment of disease are particularly heavily utilized for conditions that affect quality of life. The symptoms commonly associated with BPH have become a major target for utilization of alternative therapeutic agents. This research initiative will develop a collaborative research group to assess the efficacy of widely used alternative and complementary strategies for treatment of BPH and to compare these agents with FDA-approved drugs for the treatment of this condition.

- In September 2000, the NIDDK co-sponsored a meeting entitled "Prostate Growth and Aging." The National Institute on Aging was the primary sponsor. The goals of the conference were to ascertain the current state of knowledge in the area of prostate growth, specifically as it relates to the aging process, by inviting experts in both the basic and clinical sciences with active research in those areas; to evaluate gaps in knowledge and research; and to ascertain where future research should be emphasized. New areas for research were identified and described. This information will be used to develop future prostate research plans.

With regard to prostatitis, the Institute-supported Chronic Prostatitis Collaborative Research Network is developing and following a cohort of patients who meet the NIDDK definition of chronic prostatitis, which can be utilized to characterize the clinical and epidemiological characteristics of this disorder; and is beginning innovative therapeutic interventions in persons who meet the criteria for chronic prostatitis. In FY 2001, the Network will be expanded by addition of new clinical facilities to strengthen the recruitment of African American men with chronic prostatitis. The Network will also be expanded to allow randomized, double-blinded, placebo-controlled trials of innovative approaches to the treatment of chronic prostatitis. In October 2000, the NIDDK and the American Prostatitis Foundation hosted the third annual meeting of the International Prostatitis Collaborative Network.

Item

Urological Diseases -- The Institute held a conference two years ago to identify research issues and needs related to women's urological health. The Committee is concerned with the need for

further progress and urges the Institute to implement the conference recommendations. The Institute should be prepared to testify on the progress of this initiative at the fiscal year 2002 appropriations hearing. (p. 71)

Action Taken or to be Taken

The 1998 conference, entitled "Beyond Hunt Valley: Research for Women's Health in the 21st Century," included a discussion of urologic diseases in women--urinary incontinence, pelvic floor disorders, urinary tract infections, and interstitial cystitis. This meeting identified gaps in knowledge about these diseases, and identified priority areas of research that require further investigation.

While the NIDDK has implemented many research initiatives during the past decade with the objective of learning more about these urologic diseases in women in order to develop improved methods for diagnosing, treating and, ultimately preventing them, the conference provided impetus for further expansion of NIDDK program activities related to women's urological health. Recent examples include two FY 1999 research initiatives to enhance the scope and effectiveness of research in the area of urological diseases, and specifically to intensify investigator-initiated research, attract new investigators to the field, and increase interdisciplinary research:

- The NIDDK funded 11 research grants to study basic bladder biology and interstitial cystitis.
- The NIDDK led an NIH-wide effort to develop a network of multidisciplinary clinical centers and a biostatistical coordinating center that will focus on effective treatment strategies for women with urinary incontinence. This project will be expanded in FY 2001.

In FY 2001, the NIDDK is strengthening its efforts in several ways such as:

- Establishing a Progress Review Group for bladder diseases, which will serve as a task force for a major strategic review of current NIDDK programs in bladder research, and also to develop the future research agenda for bladder research at the NIDDK and NIH.
- Funding grants to establish a multi-center collaborative study of the epidemiology of chronic pelvic pain of bladder origin and interstitial cystitis.
- Implementing an epidemiologic study of urologic diseases, including interstitial cystitis, in the United States. Information provided from this study, called "Urologic Diseases in America," is essential to permit the NIH to effectively and efficiently plan future research in urology.
- Planning to expand its Urinary Incontinence Treatment Network to allow additional important clinical studies.
- Launching an information program, called the "Urinary Incontinence Awareness Campaign," to reach African American and Hispanic and Latino American women, especially those with diabetes.

diabetes.
- Supporting an international research symposium on interstitial cystitis and bladder research.

The NIDDK also will be working with its National Advisory Council to give special funding consideration to grants addressing women's urologic health.

Item

Urological Diseases -- The Committee remains concerned by the absence of research support for several critical areas of urology including male infertility and impotence, pediatric urology, especially congenital anomalies of the genitourinary tract, and kidney stone disease. NIDDK is urged to define the research needs and priorities in these areas as part of its overall evaluation of the urology research program. (p. 71)

Action Taken or to be Taken

In recent years, the NIDDK has supported basic research and has undertaken several research initiatives to address problems in men's urologic health. These include:
- A FY 1998 research initiative entitled "The Effect of Diabetes on the Urinary Bladder and Erectile Function." Six grants were awarded for this research.
- Support of some of the fundamental research leading to the use of sildenafil (Viagra™) for the treatment of impotence.
- Support of over 20 research grants that address the problem of kidney stone disease. The Institute sponsored a scientific workshop in December 1998 on stone disease, and convened another in November 2000 that focused on new research directions in hyperoxalosis and calcium oxalate stone disease. This meeting provided a forum for new findings in oxalate kidney stone disease, including new animal models, the role of the bacterium oxalobacter in the prevention of stone disease, tissue response to stone formation, genetics, and clinical issues.

The Institute has a research initiative planned that will examine genetic factors that may contribute to stone formation.

In addition, the NIDDK plans to consult with the urologic scientific community to define research needs and priorities in the areas of male infertility and impotence, and congenital anomalies of the genitourinary tract, and will be working with its National Advisory Council to give special emphasis to grants addressing male urological diseases research.

National Institute of Diabetes and Digestive and Kidney Diseases

SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE

SENATE

FY 2001 Senate Appropriations Committee Report Language (S. Rpt. 106-293)

Item

Behavioral and Social Science Research for Diabetes -- The Committee would like to learn more about NIDDK's plans for setting behavioral and social sciences research agenda for diabetes. In particular, the topics of diet and the prevention of obesity have prompted discussion during the Committee's hearings. According to some estimates, the prevalence of children who are overweight has nearly doubled over the past 20 years, and minority groups are disproportionately affected. NIDDK is encouraged to continue to partner with the Office of Behavioral and Social Sciences Research and other institutes, to support basic and applied research on prevention and treatment of this problem. In addition, NIDDK is encouraged to explore partnerships with other institutes on health services delivery research that can improve communication among health providers, and between health providers and their patients, to enhance treatment for diabetes. (p. 126)

Action Taken or to be Taken

Behavioral factors play a major role in the current management of diabetes and its complications. For example, the NIDDK-supported Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study demonstrated that keeping blood sugar levels as close to normal as possible slows the onset and progression of the complications caused by diabetes. In order to optimize blood glucose control with the treatments currently available, patients with diabetes must follow a tedious and complex regimen of glucose monitoring, insulin injection and/or oral medication, and strict diet regulation. Success in achieving such control is challenging and often depends on changing the behaviors of patients, physicians and those at risk for developing diabetes. The NIDDK supports substantial basic and clinical research aimed at developing successful behavioral interventions to produce sustained changes in lifestyle behaviors.

For example, the NIDDK supports research on integration of diabetes self-care management; food purchasing behavior among adults with diabetes; the role of cognitive behavior therapy in improving glycemic control; preventing depression in patients with diabetes; and the design of interventions easily implemented in primary care settings. Also, the objective of the NIDDK-supported Diabetes Prevention Program (DPP) is to prevent or delay the development of type 2 diabetes among persons at high risk using interventions designed to improve abnormal glucose metabolism. One arm of this study consists of an intensive regimen of diet and exercise. As nearly 45 percent of the study participants are from minority populations, other research questions

the DPP hopes to answer include consistency of the effects of such an intervention across ethnic, age and other subgroups and demographic, clinical, biochemical and psychosocial parameters that

predict response to this intervention.

Obesity, a major cause of morbidity and mortality in the U.S., is also a risk factor for the development of type 2 diabetes. The NIDDK supports behavioral research directly related to obesity and type 2 diabetes, including studies of appetite behavior, eating patterns, determinants of energy intake and physical activity, as well as lifestyle modification for weight loss and weight management. Acting through the NIH Nutrition Coordinating Committee, NIDDK led the development of a trans-NIH obesity prevention research initiative. We anticipate that the awards made in FY 1999 and FY 2000 will lead to the development of novel approaches to prevent obesity, particularly in minority populations and women.

The Action for Health in Diabetes (Look AHEAD) Trial, a major randomized multicenter clinical trial, will examine whether interventions such as community care and intense lifestyle changes can produce sustained weight loss in obese individuals with type 2 diabetes in order to improve health. The NIDDK will strongly encourage the recruitment of individuals from minority groups to this study because of the disproportionate burden of type 2 diabetes and obesity in the population.

In July 1999, the Diabetes Mellitus Interagency Coordinating Committee (DMICC) convened a group of epidemiologists and pediatric endocrinologists to address the alarming increase of type 2 diabetes in children, especially children from minority populations. Based on data presented at that meeting, the NIDDK and the NICHD have implemented a initiative to stimulate research on the causes, mechanisms, prevention, and treatment of type 2 diabetes in children.

The DMICC met in May 2000 with a committee of American Indian tribal leaders to exchange ideas on the problem of type 2 diabetes in American Indian children. The goal of this meeting was to foster cooperation between tribal Nations and diabetes investigators in the development of effective, culturally sensitive approaches to prevention and management of diabetes. As a result of this meeting, the NIDDK and NICHD have planned a research initiative for FY 2001 that will encourage increased research in the prevention and treatment of type 2 diabetes in minority children, with a special emphasis on children from Native American communities.

The NIDDK is also planning a number of new research initiatives over the next few years, including pilot studies on obesity therapies in minorities and clinical trials in prevention of obesity in minority populations. The later activity will begin with a workshop to assess future prevention strategies worthy of pursuit, including physical activity and social and environmental changes.

In January 2001, the NIDDK, NIMH and the NIH Office of Behavioral and Social Sciences Research will present findings on the relationship between depression and related mental disorders, and chronic diseases including diabetes, renal disease, and obesity. In cooperation with the NIA, the NIDDK will hold a meeting of the DMICC to focus on "Diabetes and Aging: From Basic Biology to Clinical Care." This meeting, to be held in January 2001, will bring together researchers in the genetic, environmental, phenotypic, and pathogenic causes of type 2 diabetes

during the aging process. It will also bring together researchers looking at diabetes health care among the elderly including disparities in diabetes treatment among minority groups during the aging process.

Item

Bladder Disease --. . . . The Committee is pleased that in 1999 the NIDDK co-sponsored the International Bladder Symposium. However, given the scope and severity of bladder diseases, the Committee continues to be very concerned about the lack of support for bladder disease research funding within the NIDDK. The Committee, therefore, urges the Institute to substantially increase its research activity into bladder diseases through all available mechanisms. The Committee further requests the issuance of a request for applications in each of the major bladder disease areas and urges the Institute to support multi-center research initiatives. The Committee requests that the Urology Program of the NIDDK, in collaboration with the bladder cancer program of the NCI establish a Bladder Disease Task Force. This Task Force is requested to make recommendations on a 3-5 year research program within the Institute to increase research into the treatments and cures for bladder diseases. The Committee further encourages the Institute to report on the establishment of the Task Force and its early recommendations during next year's hearings. (p. 126)

Action Taken or to be Taken

The NIDDK is establishing a Progress Review Group (PRG) for bladder diseases, which will serve as a task force for a major strategic review of current NIDDK programs in bladder research, and also to develop the future research agenda for bladder research at the NIDDK and NIH. The Institute envisions that the PRG will be composed of prominent members of the scientific, medical, and advocacy communities. The Institute held a preliminary meeting of the PRG in February 2001, and is planning a larger meeting to be held later in 2001.

While the bladder Progress Review Group will provide important recommendations for future directions in bladder research beginning in late FY 2001, and will address each major bladder disease specifically, the NIDDK already has implemented, expanded, or planned several research initiatives that span these diseases. For example, the NIDDK has initiated an epidemiologic study of bladder diseases and disorders, called "Urologic Diseases in America," with award anticipated for FY 2001. In addition, the Institute recently issued a Request for Applications to encourage research on the epidemiology of chronic pain of the bladder and interstitial cystitis. Awards for cooperative agreements will be made in FY 2001. Also, in FY 2001, the Institute also is planning to expand its Urinary Incontinence Treatment Network to enable additional important clinical studies.

In FY 2001, the NIDDK will launch an information program, called the "Urinary Incontinence Awareness Campaign," to reach African American and Hispanic and Latino American women, especially those with diabetes.

Item

Bone Disease –The Committee urges the Institute to focus more attention on osteoporosis and other disorders of calcium metabolism, including renal osteodystrophy, which occurs in patients

with chronic kidney disease. Nutritional and hormonal influences on calcium and skeletal status should also receive increased attention, as should functional genomics in bone. The Committee also urges the Institute to work with the National Cancer Institute to focus on cancer that spreads to bone. (p.126-127)

Action Taken or to be Taken

Please refer to page 36 of this document for NIDDK's response to this significant item regarding "Bone Diseases."

Item

Cooley's anemia --. . . . The Committee urges the institute to acquire this technology for use in an intramural research protocol testing its efficacy with Cooley's anemia patients, while pursuing opportunities to improve the equipment through the use of advanced materials and computer applications. In addition, the Committee remains interested in the research progress being made with regard to the development of safe and effective iron chelator drugs that are less troublesome than those currently used, as well as the development of drugs for the regulation of hemoglobin synthesis. (p. 127)

Action Taken or to be Taken

Please refer to page 38-39 of this document for NIDDK's response to this significant item regarding "Cooley's Anemia."

Item

Diabetes in Hispanic Populations. -- Hispanic Americans are disproportionately affected by diabetes, with over 1.8 million affected by this disease. The Committee encourages the Institute to undertake efforts to include this population in NIH studies and to expand research to understand why diabetes disproportionately affects this population. (p.127)

Action Taken or to be Taken

Type 2 diabetes, the form most commonly seen in the Hispanic community, occurs at a rate approximately twice that in the non-Hispanic Caucasian population. Identification of the genes involved in diabetes is important because gene discovery is a major step leading to early diagnosis, prevention, and improved treatments for diabetes. The NIDDK supports the San Antonio Family Diabetes Study (SAFADS) in which investigators hope to identify the genes that might result in

increased susceptibility to developing type 2 diabetes. Researchers have enrolled over 500 Mexican Americans from 31 families. Recently, a gene responsible for type 2 diabetes has been identified in the Mexican American population from Starr County, Texas.

The International Type 2 Diabetes Linkage Analysis Consortium originated in 1997 as a

collaborative effort to map genes responsible for type 2 diabetes. This Consortium is jointly funded by the NIH and the American Diabetes Association. Currently, the Consortium includes investigators representing 24 patient groups from five countries. Locations in San Antonio and Starr County (Texas), and San Luis Valley (Colorado) include Mexican American families in the genetic linkage analysis.

The Family Investigation of Nephropathy and Diabetes (FIND) is investigating genetic loci associated with the presence and severity of diabetic kidney disease in Caucasian, African American, Hispanic, and Native American populations across the United States. The NIDDK plans to expand this study in FY 2001 to include more minority subjects and to include useful comparisons of nephropathy susceptibility loci in the well-characterized patients and their families from the African Americans Study of Kidney Disease and Hypertension (AASK) Trial.

The NIDDK has also taken steps to ensure appropriate representation of minority populations, such as Hispanic Americans, in clinical trials on diabetes. The Diabetes Prevention Program (DPP) is designed to find out whether type 2 diabetes can be delayed or prevented. The DPP has completed recruitment of over 3,800 participants–nearly 45 percent of whom are minorities. Of the over 3,800 participants, 609 (16 percent) are of Hispanic origin, including Mexican Americans, Puerto Ricans, and Cuban Americans. The Action for Health in Diabetes (Look AHEAD) trial is designed to study if interventions to produce weight loss in obese individuals with type 2 diabetes will improve health. Investigators will analyze both fatal and non-fatal occurrences of heart attacks and strokes. The Look AHEAD is expected to recruit approximately 6,000 patients with an overall ethnic and racial composition to reflect the prevalence rates for diabetes in the United States. It is expected that Look AHEAD will include participants from a wide range of Hispanic populations. The NIDDK has also issued announcements to solicit research on expanding our understanding of mechanisms that contribute to racial and ethnic differences in the susceptibility to diabetes and on disparities in the risk of developing diabetes complications.

Type 2 diabetes has traditionally been considered a disease of adults. In recent years, however, an increasing number of children are being diagnosed with type 2 diabetes. In July 1999, the Diabetes Mellitus Interagency Coordinating Committee convened a group of epidemiologists and pediatric endocrinologist to address the alarming rise in the incidence of type 2 diabetes in children, especially children from in minority populations–Hispanic Americans, African Americans and Native Americans. The NIDDK issued a solicitation encouraging research that will lead to a new understanding of why diabetes is occurring at increasingly younger ages in minority populations and to encourage new approaches to prevent and treat type 2 diabetes in at-risk children. Applications received in response to this solicitation have been reviewed and the awards will include studies in Hispanic populations. This research initiative is co-sponsored by

National Institute of Child Health and Human Development (NICHD). In FY 2001, the NIDDK plans to support a research initiative on the prevention and treatment of type 2 diabetes in minority children to further increase research in this area.

Complementing the many basic and clinical diabetes research programs of the NIH are critically important diabetes education and information programs--built on science-based messages. The National Diabetes Education Program (NDEP) is a joint undertaking of the NIH and the CDC, with

over 150 public and private partners--including several Hispanic organizations. The NDEP has also targeted Hispanic audiences with culturally-sensitive public health messages tailored by minority organizations who belong to the NDEP Partnership. The Hispanic/Latino campaign has won an Award of Excellence from the Health Improvement Institute, as well as the 1998 Silver Mercury Award from the International Academy of Communications, Arts and Sciences/MerComm, Inc. Complementing these education campaigns are the efforts of the National Diabetes Information Clearinghouse (NDIC), established to increase knowledge and understanding about diabetes among patients, health care professional, and the public. Many fact sheets and pamphlets about diabetes are available in Spanish formats.

Item

Digestive Disease Centers -- . . . . . The Committee continues to encourage NIDDK to expand this important program, with an increased emphasis on inflammatory bowel disease. (p.128)

Action Taken or to be Taken

Please refer to page 45-46 of this document for NIDDK's response to this significant item regarding "Inflammatory Bowel Disease."

Item

Digestive Diseases -- .... The Committee continues to encourage NIDDK to give priority consideration to the following areas of IBD research: (1) investigation into the cellular, molecular and genetic structure of IBD, (2) identification of the genes that determine susceptibility or resistance to IBD in various patient subgroups, and (3) coordination and integration of basic investigations designed to clarify mechanisms of action and disease pathogenesis into clinical trials, as described in the research agenda developed by the scientific community entitled "Challenges in Inflammatory Bowel Disease." (p. 128)

Action Taken or to be Taken

Please refer to pages 43 & 45-46 of this document for NIDDK's response to this significant item regarding "Digestive Diseases" and "Inflammatory Bowel Disease."

Item

End-stage renal disease -- The Committee understands that recent studies suggest that patients with end-stage kidney disease are far more likely to have close family relatives with kidney disease. Certain ethnic populations in America also have an increased risk of kidney disease. Hispanics in the western United States have a four-fold increased likelihood over Caucasian and Asian-Americans for end-stage renal disease requiring dialysis. The increased likelihood for African-Americans is at least six-fold and in certain urban areas the likelihood is far greater. The Committee encourages the

NIDDK to take advantage of these "familial clusters" to create a kidney genome anatomy program and to consider funding projects to make and sequence DNA libraries from normal and diseased tissues. The Committee also encourages NIDDK to supply and implement the bioinformatics required to link the gene fragments with gene names in NIH supported databases, and to provide this information, with access to the clones, to the scientific community. (p. 128)

Action Taken or to be Taken

Please refer to page 48-49 of this document for NIDDK's response to this significant item regarding "Kidney Genome Anatomy Program."

Item

Hepatitis C -- The Committee is aware that little is understood about the mechanisms that lead to the transition of acute hepatitis C into its more chronic forms. Little is also known about the most appropriate time to begin treatment of those with hepatitis C to prevent the progression of the disease. The Committee encourages the Institute to invest additional resources into the causes and treatments of this disease. (p. 128)

Action Taken or to be Taken

The NIDDK plans to co-fund ancillary studies with NIAID and industry based on a large scale clinical trial on hepatitis C -- the HALT-C trial. The studies connected with the trial will use data collected before, during and after therapy, to direct research in such areas as the non-invasive assessment of liver fibrosis; how hepatitis C virus replicates; risk factors for progression, including nutrition, obesity, smoking, and alcohol; and the role of genetic diversity in diagnosis and clinical management of hepatitis C. The Institute also is planning a research initiative to address "Hepatitis C in African Americans" for FY 2001 to follow-up on a 1999 meeting on this topic sponsored by NIDDK in collaboration with the National Center for Minority Health and Health Disparity, National Institute of Allergy and Infectious Diseases (NIAID), National Cancer Institute (NCI), National Institute on Drug Abuse (NIDA) and the Centers for Disease Control and Prevention (CDC). Three interrelated Requests for Applications will ask for grant applications to conduct a clinical study of antiviral therapy in chronic hepatitis C that will include equal numbers of African Americans and non-Hispanic whites. The focus of the study will be viral kinetics

during therapy as well as specialized studies of virology and host genomics to help define the phenotype of resistance to interferon therapy that is extremely common among African Americans with hepatitis C.

Item

Hepatitis C -- . . . .the HALT C trial, is expected to yield important scientific discoveries, and offer opportunities for ancillary studies regarding the relatively low response rate to current hepatitis C treatments. Those ancillary studies could include the influence of genetic factors, the rate and cause of viral mutations, and the wide range of reactions of hepatitis C patients to treatment protocols.

The Committee urges NIDDK to provide the funding necessary to pursue these ancillary research opportunities. (pp. 128-129)

Action Taken or to be Taken

Please refer to page 44 of this document for NIDDK's response to this significant item regarding "Hepatitis C."

Item

Hereditary Hemochromatosis --. . . . The Committee urges the Institute to expand its research portfolio on this disease, particularly as it relates to early diagnosis. (p. 129)

Action Taken or to be Taken

There is a pressing need to be able to perform non-invasive measurements of body iron stores in order to diagnose and monitor treatment for patients with transfusion-related iron overload and possibly for individuals with hemochromatosis mutations. The NIDDK is planning a scientific workshop in FY 2001 to evaluate a number of potential methods for the noninvasive measurement of body iron load, including SQUID (superconducting quantum interference device) and MRI. The workshop is intended to advance the technology and to assist the NIDDK in making decisions on needed research initiatives in this research area.

The NIDDK also has implemented two hemochromatosis research initiatives in collaboration with the National Heart, Lung, and Blood Institute. A FY 1999 research initiative resulted in NIDDK funding new grants to study the biology of iron overload, including hereditary hemochromatosis, and new innovative approaches to therapy. The NIDDK is awaiting receipt of grant applications from a FY 2000 research initiative on hemochromatosis and diabetes.

Item

Hypertension and Kidney Disease -- The Committee is concerned that NHLBI is not currently funding or collaborating with the NIDDK on any research projects related to hypertension and its relationship to kidney disease. Given that hypertension is the number two cause of kidney disease

it would seem appropriate for the NHLBI to have this as a priority area. The Committee urges the NIDDK and the NHLBI to sponsor a workshop in collaboration with the renal community to define areas and research questions for a series of joint requests for applications by the NIDDK and NHLBI targeted at hypertension and kidney disease. The Director of the Institute should be prepared to testify on the progress in this area at the fiscal year 2002 appropriations hearings. (p. 129)

Action Taken or to be Taken

Please refer to page 44-45 of this document for NIDDK's response to this significant item regarding "Hypertension and Kidney Disease."

Item

Interstitial cystitis --. . . . The Committee encourages NIDDK to undertake a more aggressive approach to this chronic, debilitating disease. The Committee is pleased that the NIDDK has initiated in fiscal year 2000 a study of the epidemiology of the disease, and requests the Institute report to the Committee during next year's hearings on the status of this research initiative. The Committee encourages the Institute to increase research into the basic and clinical aspects of interstitial cystitis and to establish centers which have a significant minority enrollment. (p. 129)

Action Taken or to be Taken

Please refer to page 46-47 of this document for NIDDK's response to this significant item regarding "Interstitial Cystitis."

Item

Irritable bowel syndrome-- . . . .The Committee encourages NIDDK to increase funding for irritable bowel syndrome/functional bowel disorders research and to give priority consideration to funding IBS education/scientific symposiums. (pp. 129-130)

Please refer to page 46 of this document for NIDDK's response to this significant item regarding "Irritable Bowel Syndrome."

Item

Kidney disease --. . . . the Committee encourages the NIDDK to expand its Diabetes Genome Anatomy Project to include a focus on the kidney disease that is a major complication of diabetes. (p. 130)

Action Taken or to be Taken

Please refer to page 48-49 of this document for NIDDK's response to this significant item regarding "Kidney Genome Anatomy Program."

Item

Kidney disease education -- The Committee urges the NIDDK to plan and implement a National Kidney Disease Education Project. Given that there are some ways to slow the progress of kidney disease if it is identified early, NIDDK is urged to launch an effort to reach out to the more than 12 million Americans living with chronic renal insufficiency. These individuals are often unaware that they suffer from this disease until they have already reached end-stage renal disease and require dialysis or a transplant. The Committee urges the NIDDK to bring these advances in medical care to the consumers. The Director of the Institute should be prepared to testify on the progress of this initiative at the fiscal year 2002 appropriations hearings. (p. 130)

Action Taken or to be Taken

Please refer to page 47-48 of this document for NIDDK's response to this significant item regarding "Kidney Disease Education."

Item

Liver Transplantation Conference-- The Committee is aware of the significant and continuing shortage of livers available for transplantation, and therefore urges additional research that would facilitate the success of liver transplantation and the number of livers available for transplantation. Many believe that the use of living liver donors may be one of the most important surgical and scientific breakthroughs that can assist people in the need of liver transplants. (p. 130)

Action Taken or to be Taken

Please refer to page 49 of this document for NIDDK's response to this significant item regarding "Liver Transplantation."

Item

Cushing's Syndrome -- The Committee encourages the Institute to conduct specific research on Cushing's Syndrome, to increase awareness of the disease and improve diagnostic tools and treatment. (p. 154)

Action Taken or to be Taken

Cushing's syndrome occurs when the adrenal glands produce excessive amounts of a hormone product of the adrenal–cortisol–that is needed to sustain life. There are many causes of Cushing's syndrome, including tumors of adrenal glands or the pituitary gland, certain tumors of the lung, and long-term use of glucocorticoid hormones for the treatment of inflammatory diseases such as asthma, rheumatoid arthritis and lupus. Due to the many and diverse conditions that may cause Cushing's syndrome, and the wide-ranging nature of the complications, several components of the NIH conduct and support research on this syndrome, including the National Institute of Diabetes

and Digestive and Kidney Diseases (NIDDK), the National Institute of Child Health and Human Development (NICHD), the National Institute of Neurological Disorders and Stroke (NINDS), and the National Cancer Institute (NCI).

NIH-supported scientists are conducting research into the normal and abnormal function of the major endocrine glands and the many hormones of the endocrine system. Improved technologies have led to the identification of certain hormones that play a significant role in the development of Cushing's syndrome. As a result, doctors are much better able to diagnose Cushing's syndrome and distinguish among the many causes of this disorder. For example, by taking a sample of blood from the small veins that drain blood from the pituitary gland, doctors can determine whether Cushing's syndrome is due to a tumor in the pituitary gland or a tumor elsewhere in the body. However, the procedure to collect blood is very difficult to perform and is only available in a few hospitals. Therefore, NIH researchers are looking for other ways to diagnose this disease that would be less technically difficult and more readily available to patients.

Many studies are also underway to understand the causes of formation of benign endocrine tumors, including those which cause Cushing's syndrome. In a few pituitary adenomas, specific gene defects have been identified and may provide important clues to understanding tumor formation. There is increasing evidence that tumor formation is a multi-step process. Understanding the basis of Cushing's syndrome will yield new approaches to therapy.

Item

Non-Alcoholic Steatohepatitis -- . . . . The Committee urges research into the cause or pathogenesis of this disease as well as research on treatments. (p. 130)

Action Taken or to be Taken

Non-alcoholic steatohepatitis (NASH) is a liver disease that is becoming "epidemic" in the U.S. and is found commonly in patients with diabetes and obesity. To address this health problem, a Program Announcement will be issued in FY 2001 that will ask for research project grants or planning grants on the mechanisms and progress of liver injury in NASH. In addition, the NIDDK plans to launch a clinical trial network with NASH as its first area of focus.

Item

Pediatric kidney disease -- . . . .the Committee encourages NIDDK to enhance its research efforts into the prevention and treatment of chronic renal failure and end-stage renal disease in children from all causes, including diabetes, hypertension, genetic kidney disease and disorders of renal

development. NIDDK also is urged to focus on new approaches to enhance or accelerate recovery from acute renal failure, which commonly occurs in hospitalized pediatric patients and accounts for substantial sickness and death. (p. 130/131)

Action Taken or to be Taken

Please refer to page 50-51 of this document for NIDDK's response to this significant item regarding "Pediatric Kidney Disease."

Item

Polycystic kidney disease --. . . . It is the Committee's strongest recommendation that the PKD Strategic Plan, developed at NIDDK in early fiscal year 1999, be implemented and fully funded as expeditiously as possible. Anything less places in greater jeopardy many of the 600,000 Americans with this devastating disease whose kidneys are still functioning, the ones for whom a treatment to stop the progression of PKD may well mean the avoidance of kidney failure and its devastating consequences. (p. 131)

Action Taken or to be Taken

Please refer to page 51 of this document for NIDDK's response to this significant item regarding "Polycystic Kidney Disease."

Item

Prescription and Non-Prescription Medications and Acute Liver Failure -- The Committee is aware that the most common cause of acute liver failure is a reaction to over-the-counter and prescription medications. With the aging of the population, and consequently more and more Americans using multiple medications, NIDDK is urged to pursue additional research to isolate the causes of adverse reactions to medications. (p. 131)

Action Taken or to be Taken

NIDDK held a two-day research workshop on "New Directions in Drug-Induced Liver Injury: Mechanisms and Test Systems" on October 17-18, 2000. This workshop focused on mechanisms of hepatotoxicity with clinical-pathological correlations. The forum encouraged debate and highlighted future research needs, in particular, the most effective means to build a research portfolio in a difficult area that is commensurate with its growing importance. It is expected that a Request for Applications will result based on the recommendations of the participants. A likely focus will be basic research on specific hepatotoxins or pathways of drug-induced liver injury or development of multidisciplinary grants in this area. Other possible avenues of research effort include a database on patients with hepatotoxicity and specific research projects based upon serum, tissue, cells and DNA from well-characterized cases.

Item

Prostatitis -- The Committee is pleased that the NIDDK has recognized prostatitis as one of the three major diseases of the prostate gland. The Committee continues to encourage efforts to more aggressively explore the relationship among these diseases of the prostate. . . . The Committee believes there is mounting evidence that prostatitis is a worldwide problem and that millions of American men suffer from the disease. The Committee further encourages more solicitation of individual applications from investigators with diverse backgrounds to address clinical research approaches. Including representatives from NCI, NINDS, NINR, and outside medical consultants from diverse speciality backgrounds. The Committee recommends that NIDDK add two more centers to support this work. The Committee also urges the Institute to expand its studies of various minority groups, and encourages expanded outreach efforts that include educational materials directed at primary care physicians, the urology community, patients and the general public. (p. 131)

Action Taken or to be Taken

Please refer to page 51-52 of this document for NIDDK's response to this significant item regarding "Prostatitis."

FY 2001 CONFERENCE REPORT NO. 106-1033

SIGNIFICANT ITEMS

National Institutes of Health

Item

[Urology research] -- The conferees are concerned that the urology research effort is not addressing the large public health impact of urological diseases and conditions. NIDDK is strongly urged to enhance its research initiatives in urology. p. 135.

Action Taken or to be Taken

The National Institute of Diabetes and Digestive and Kidney Diseases is very much aware of the serious health impact that urologic diseases have on the U.S. population, and has over the last decade greatly enhanced research efforts in this regard. In FY 2001 alone, the NIDDK has implemented several new or expanded research initiatives that address urologic diseases. These include:

1. EPIDEMIOLOGY OF UROLOGIC DISEASES IN AMERICA
This new research initiative will delineate the changes in the epidemiology, health economic impact, and practice patterns for each of the diseases currently included within the scope of practice of the specialty of urology, analyzed retrospectively over a ten-year period. This database would, for the first time, give realistic estimates of the extent of and health care expenditures for these diseases, the variations in treatments, and the effect that these diseases have on minority populations. Such information is essential to permit the NIH to effectively and efficiently plan future research in urology.

2. STUDIES ON HEREDITARY STONE DISEASE
This research initiative is encouraging pilot and feasibility studies that utilize new and innovative approaches to the study of hereditary stone disease.

3. EPIDEMIOLOGY OF CHRONIC PELVIC PAIN OF THE BLADDER AND INTERSTITIAL CYSTITIS
This initiative will establish a multi-center collaborative study of the epidemiology of chronic pelvic pain of bladder origin and interstitial cystitis. The goals are to determine the prevalence, incidence, risk factors, quality of life, functional status, and health resource utilization for interstitial cystitis and chronic pelvic pain of bladder origin in men, women, and children.

4. PROGRESS REVIEW GROUP FOR BLADDER RESEARCH
The NIDDK is establishing a Progress Review Group (PRG) for bladder research, which will serve as a task force for a major strategic review of current NIDDK programs in bladder research, and also to develop the future research agenda for bladder research at the NIDDK and NIH.

Prominent members of the scientific, medical, and advocacy communities will comprise the PRG.

The Institute convened a preliminary meeting of the PRG in February 2001, and plans to hold a larger meeting later in 2001.

5. INNOVATIVE THERAPEUTIC INTERVENTIONS FOR CHRONIC PROSTATITIS, AND MINORITY RECRUITMENT IN CHRONIC PROSTATITIS COHORT STUDY

This research initiative is expanding the Institute's ongoing Chronic Prostatitis Collaborative Research Network. Established in 1997, the Network is a consortium of six clinical centers and a data coordinating center. The expansion will provide resources for testing innovative approaches to the treatment of chronic prostatitis. This study also is testing diagnostic criteria that will clarify the definition of the chronic prostatitis, and is following a cohort of patients to establish the natural history of this condition. The Network is also being expanded by adding new clinical facilities to strengthen the recruitment of African American men with chronic prostatitis.

6. URINARY INCONTINENCE AWARENESS CAMPAIGN

The NIDDK's National Kidney and Urologic Diseases Information Clearinghouse is launching a coordinated information program to reach African American, Hispanic and Latino American women, especially those with diabetes. This research initiative will enable the NIDDK to extend its reach to public and private partners to develop culturally-sensitive materials pertaining to bladder control; attend additional professional meetings at which incontinence publications may be promoted; and promote the availability of free bladder control information in publications for minority audiences.

7. ALTERNATIVE AND COMPLEMENTARY THERAPIES FOR SYMPTOMATIC BENIGN PROSTATIC HYPERPLASIA

The use of alternative, plant-derived therapeutic approaches for the relief of the symptoms of benign prostatic hyperplasia (BPH) is increasing. The goal of this research initiative is to determine the clinical and physiological effects of the most commonly used plant-derived agents. A consortium of basic and clinical investigators will be established to evaluate which symptoms associated with BPH are modified by these agents, the duration of the effect, the effect on prostate tissue and the urinary bladder, and serum hormone and prostate markers such as prostate-specific antigen and testosterone.

8. EXPANSION OF NIDDK URINARY INCONTINENCE TREATMENT NETWORK CLINICAL CENTERS

In FY 2000, the NIDDK began the development of a Urinary Incontinence Treatment Network by supporting four clinical centers and one statistical center. In FY 2001, the number of clinical centers will be expanded.

The NIDDK is also planning several new or expanded urology research initiatives for FY 2002.

Item

[Studying cellular glucose metabolism] – The conferees encourage NIDDK to coordinate with the Office of Dietary Supplements on their findings from the chromium and diabetes nutrition conference held in November of 1999. The Institute is encouraged to enhance basic research grants to examine cellular glucose metabolism and the factors that influence that metabolism, especially the influence of chromium-containing compounds on glucose receptors. p. 135

Action Taken or to be Taken

In vitro studies have suggested that chromium may enhance insulin sensitivity, although its mechanism of action is poorly understood. Several small clinical studies have reported improved glycemic control in patients with diabetes. For the most part, however, these studies have not been well controlled. Little is known about the chromium status of patients with diabetes, in part because validated measures of whole body chromium have not been established. In addition, further information regarding bioavailability and toxicity is needed for oral chromium preparations. The NIDDK, the National Center for Complementary and Alternative Medicine, and the Office of Dietary Supplements are planning a research initiative for FY 2002 to encourage basic and clinical research on the effect of chromium on insulin action. The activity would solicit basic research to enhance understanding of the mechanism of action of chromium on insulin binding, signaling, and action. In addition, it would support clinical research to investigate appropriate dose and formulations for chromium supplementation in diabetes, to provide safety data, and to develop clinically relevant biomarkers that could potentially be useful in clinical trials of chromium supplementation for diabetes.

Item

[Mucopolysaccharidosis (MPS)] – The conferees encourage NIDDK to expand research efforts for treatments for mucopolysaccharidosis. The conferees recognize the recent progress in some areas of MPS research, however, the persistent challenges in development of effective treatments remain. NIDDK is encouraged to work with other Institutes, especially NINDS and NICHD, to research effective therapies. p. 135

Action Taken or to be Taken

The NIDDK provides support for research on MPS and other lysosomal storage diseases. Research on treatment approaches currently supported by the Institute include enzyme replacement therapy, bone marrow transplantation, substrate deprivation, and gene therapy. NIDDK support for MPS research increased from $2.5 million in FY 1999 to $3.12 million in FY 2000 and is expected to increase further in FY 2001. In FY 2001, the NIDDK has already funded three new MPS research projects. The Institute will continue to encourage research to develop treatments for genetic metabolic diseases through the Small Business Innovation Research (SBIR) mechanism. NIDDK staff also participated in planning the upcoming "Fourth National Gene Transfer Safety Symposium: Safety Consideration in the Use of AAV Vectors in Gene Transfer Clinical Trials," which is a part of ongoing Departmental efforts to ensure patient protection in gene therapy. Included in the major topics for discussion at the safety symposium are the MPS VII mouse model results, and other clinical and preclinical data to date.

In FY 2000, the NICHD supported 18 projects on mucopolysaccharidoses for a total of $1.4 million. Most of these studies deal with developing different approaches to treat this group of conditions. Therapeutic approaches include enzyme replacement therapy with or without bone marrow transplantation, gene therapy in animal models using adenoviral and adenoassociated viral vectors, lentivirus hematopoietic stem cell gene therapy in animal models, and functional studies to determine the outcome after enzyme therapy in animal models. No human subjects are involved in these studies.

The NIDDK, NINDS, and NICHD have held discussions with the representatives from the National Mucopolysaccharidosis (MPS) Society in an effort to identify the optimal means to stimulate research, including the possibility of a workshop that would bring together researchers who would explore the relevant issues.

Item

[Interdisciplinary Research Center] -- The conferees are concerned regarding reports that funding for two of the four recently established Interdisciplinary Research Centers have been significantly reduced. The conferees urge NIDDK, consistent with the PKD Strategic Plan, to fully fund the four Interdisciplinary Research Centers. pp. 135/136.

Action Taken or to be Taken

The NIDDK has recently instituted a number of adjustments in funding its research centers, including the Polycystic Kidney Disease (PKD) Interdisciplinary Research Centers. One of the adjustments is to fully fund all four PKD Centers. It is anticipated that this enhanced investment will provide an excellent opportunity for the Centers to succeed in achieving their stated goals.

Item

[Inflammatory bowel disease (IBD)] – The conferees are pleased with the growth of the NIDDK research portfolio on IBD and the focus on IBD in several of the Institute's digestive diseases centers. Moreover, several new research initiatives are planned, including efforts to create an IBD genetics consortium in followup to a meeting NIDDK held in March 2000 on the genetics of IBD. The conferees are hopeful that IBD will be one of the diseases to be studied in the soon-to-be-established NIDDK digestive diseases trial network. The conferees urge the Institute to foster research on genetic, environmental and other factors that offer promise of shedding light on the underlying causes of immunologic abnormalities and inflammatory mechanisms in IBD, and that may help point the way to more effective therapeutic and preventive strategies. p. 136.

Action to be Taken

NIDDK is planning an interdisciplinary scientific workshop in 2001 to address current concepts in the development of IBD, including the role of immune and genetic factors. One result of this meeting likely will be the implementation of a research initiative in FY 2002 for a genetics of IBD research consortium and an IBD clinical research network.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2000 Amount Authorized	2001 Estimate	2002 Amount Authorized	2002 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite		Indefinite	
National Institute of Diabetes and Digestive and Kidney Diseases	Section 426	42§285c	Indefinite	$1,264,656,000	Indefinite	$1,414,838,000
Research on Osteoporosis, Paget's Disease and Related Bone Disorders	Section 409A	42§284e		----		----
National Research Service Awards	Section 487(d)	42§288	a/	39,161,000	b/	43,077,000
Total, Budget Authority				1,303,817,000		1,457,915,000

a/ Funding provided under the Departments of Labor, Health and Human Services, Education, and Related Agencies Act, 2001 (P.L. 106-554).

b/ Reauthorizing legislation will be submitted.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Appropriation History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1993	$699,809,000	$688,633,000	$688,633,000	$681,342,000 2/
1994	677,135,000	716,054,000	716,054,000	716,054,000
1995 3/	731,500,000	726,784,000	728,784,000	727,628,000 4/
Rescission				(679,000)
1996	748,798,000 3/	771,252,000	738,456,000 3/	771,252,000 5/
Rescission				(670,000)
1997	758,847,000 3/	806,542,000	787,473,000 3/	815,607,000 6/
1998	821,164,000 3/	874,337,000	883,321,000	873,860,000
1999	924,702,000 3/,7/	951,203,000	994,218,000	994,218,000
Rescission				(659,000)
2000	1,002,747,000 3/	1,087,455,000	1,130,056,000	1,147,588,000 8/
Rescission				(6,112,000)
2001	1,186,266,000 3/	1,315,530,000	1,318,106,000	1,303,385,000 9/
Rescission				(429,000)
2002	1,457,915,000			

1/ Reflects enacted supplements, rescissions, reappropriations, and reductions.

2/ Excludes enacted administration reductions of $7,291,000.

3/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.

4/ Excludes enacted administration reduction of $679,000.

5/ Excludes enacted administration reduction of $670,000.

6/ Excludes enacted administration reduction of $375,000.

7/ Reflects a decrease of $2,790,000 for the budget amendment for bioterrorism.

8/ Excludes enacted administration reduction of $6,112,000.

9/ Excludes enacted administration reduction of $429,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2000 Actual	FY 2001 Estimate	FY 2002 Estimate
Office of the Director	64	76	78
Division of Diabetes, Endocrinology and Metabolic Diseases	19	25	27
Division of Digestive Diseases and Nutrition	16	20	21
Division of Kidney, Urologic and Hematologic Diseases	15	19	20
Division of Nutrition Research Coordination	6	6	7
Division of Extramural Activities	60	60	60
Division of Intramural Research	419	421	436
Total, NIDDK	599	627	649
FTEs supported by funds from Cooperative Research and Development Agreements	(0)	(2)	(2)

FISCAL YEAR	Average GM/GS Grade
1998	10.8
1999	10.9
2000	11.0
2001	11.0
2002	11.0

NATIONAL INSTITUTES OF HEALTH
National Institute of Diabetes and Digestive and Kidney Diseases
Program Administration

Detail of Positions

GRADE	FY 2000 Actual	FY 2001 Estimate	FY 2002 Estimate
ES-6	0	0	0
ES-5	1	1	1
ES-4	4	4	4
ES-3	0	0	0
ES-2	0	0	0
ES-1	0	0	0
Subtotal	5	5	5
Total - ES Salary	$651,000	$683,550	$717,730
GM/GS-15	48	50	50
GM/GS-14	59	63	63
GM/GS-13	49	55	57
GS-12	47	50	54
GS-11	42	43	45
GS-10	4	5	5
GS-9	43	48	50
GS-8	34	37	39
GS-7	45	51	53
GS-6	12	13	14
GS-5	7	9	9
GS-4	4	4	5
GS-3	2	2	3
GS-2	1	1	0
GS-1	0	0	0
Subtotal	397	431	447
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	0	0	1
Director Grade	17	21	19
Senior Grade	6	7	8
Full Grade	4	5	6
Senior Assistant Grade	0	0	1
Assistant Grade	0	0	0
Co-Step	0	0	0
Subtotal	27	33	35
Ungraded	174	178	182
Total permanent positions	401	433	445
Total positions, end of year	603	647	669
Total full-time equivalent (FTE) employment,end of year	599	627	649
Average ES level	ES-4	ES-4	ES-4
Average ES salary	$130,200	$136,710	$143,546
Average GM/GS grade	11.0	11.0	11.0
Average GM/GS salary	$60,147	$63,154	$66,312

NATIONAL INSTITUTES OF HEALTH
National Institute of Diabetes and Digestive and Kidney Diseases

New Positions Requested

	FY 2002		
	Grade	Number	Annual Salary
Health Science Administrator	GS-15	5	$99,580
	GS-14	5	84,658
Public Affairs Specialists	GS-12	1	60,242
Administrative Officers	GS-12	2	60,242
Grants Management Specialis	GS-11	2	50,265
	GS-7	1	33,961
Purchasing Agent	GS-8	1	37,614
Secretaries	GS-7	2	33,961
Administrative Technician	GS-7	1	33,961
Grants Technical Assistant	GS-7	2	33,961
Total Requested		22	